THE NATION'S FLU SHOT SHORTAGE: WHERE ARE WE TODAY AND HOW PREPARED ARE WE FOR TOMORROW?

HEARING

BEFORE THE

COMMITTEE ON GOVERNMENT REFORM

HOUSE OF REPRESENTATIVES

ONE HUNDRED EIGHTH CONGRESS

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THE NATION'S FLU SHOT SHORTAGE: WHERE ARE WE TODAY AND HOW PREPARED ARE WE FOR TOMORROW?

WEDNESDAY, NOVEMBER 17, 2004

HOUSE OF REPRESENTATIVES,
COMMITTEE ON GOVERNMENT REFORM,
Washington, DC.

The committee met, pursuant to notice, at 1:05 p.m., in room 2154, Rayburn House Office Building, Hon. Tom Davis (chairman of the committee) presiding.

Present: Representatives Davis, Shays, Mica, Duncan, Deal, Murphy, Waxman, Lantos, Owens, Towns, Sanders, Maloney, Cummings, Kucinich, Tierney, Clay, Watson, Van Hollen, Ruppersberger, Norton, Cooper, and McCollum.

Staff present: Melissa Wojciak, staff director, David Marin, deputy staff director/communications director; Keith Ausbrook, chief counsel; Ellen Brown, legislative director and senior policy counsel; Jennifer Safavian, chief counsel for oversight and investigations; Anne Marie Turner, counsel; Robert Borden, counsel/parliamentarian; Robert White, press secretary; Drew Crockett, deputy director of communications; Susie Schulte, professional staff member; Teresa Austin, chief clerk; Sarah Dorsie, deputy clerk; Allyson Blandford, office manager; Corinne Zaccagnini, chief information officer; Phil Barnett, minority staff director; Kristin Amerling, minority deputy chief counsel; Karen Lightfoot, minority communications director/senior policy advisor; Anna Laitin, minority communications and policy assistant; Sarah Despres and Naomi Seller, minority counsels; Richard Butcher and Josh Sharfstein, minority professional staff members; Earley Green, minority chief clerk; and Jean Gosa, minority assistant clerk.

Chairman TOM DAVIS. Good morning. A quorum being present, the Committee on Government Reform will come to order. I want to welcome everybody to today's oversight hearing regarding this year's U.S. influenza vaccine supply.

As most are now aware, on October 5, 2004, the Medicines and Healthcare Products Regulatory Agency, United Kingdom's version of the U.S. Food and Drug Administration, suspended Chiron Corp.'s manufacturer's license for a period of 3 months. Chiron planned on delivering 46 to 48 million doses of flu vaccine, almost half of the U.S. supply.

This committee's investigation into the issues surrounding the flu vaccine shortage began at a flu pandemic hearing in February of this year. The committee informed U.S. health officials of its con-

cern that Chiron did not have a manufacturing plant located within the United States. So should a flu pandemic occur, it was theorized that the U.K. could nationalize Chiron's vaccine supply, resulting in the loss of half of our national supply.

At an emergency hearing on October 8, 2004, the committee discussed contributing factors to the flu vaccine shortage, how the government and vaccine manufacturers were responding to and managing the crisis, and what steps would be taken to prepare for next year's flu season.

As a result of testimony at these two hearings, Ranking Member Henry Waxman and I sent a letter to the FDA requesting documents that would indicate whether FDA knew about the problems at the Chiron facility and whether FDA responded adequately.

As part of this committee's investigation, I led a congressional delegation to London last week to meet with top-ranking officials from the MHRA and Chiron. The committee also conducted an extensive meeting with FDA officials in Washington to discuss FDA documents and the committee's findings from meetings held in London. These meetings were extremely productive, provided the committee with a timeline of events leading up to October 5, 2004 the standard protocols used by MHRA and FDA, and the steps all parties involved are taking to prevent future vaccine shortages.

The FDA documents and investigative meetings held by the committee confirmed several key facts. First and foremost, FDA was unaware prior to October 5, 2004 that MHRA would suspend Chiron's manufacturing license.

On October 25, 2004, Chiron contacted the FDA to alert the agency there may be a delay in its vaccine shipment, as contamination was located in some lots of Chiron's flu vaccine. All documents and meetings confirm that FDA followed routine protocol in responding to Chiron's initial contact with FDA and continued to follow protocol with each step the agency took after October 25th.

Chiron also notified FDA that it had conducted an internal failure investigation to discover how the contamination occurred. It is standard protocol for FDA to have a manufacturer's failure investigative report in hand when conducting an inspection. The FDA uses that report in determining cause and the report serves as a roadmap for the inspection. Chiron informed FDA that it would receive the internal report the week of October 4, 2004. FDA has informed the committee that it believed this was a reasonable timeframe. During this time, FDA was in constant communication with officials from Chiron and immediately alerted the Centers for Disease Control and Prevention about the delay in Chiron's shipment.

Unfortunately, the internal report was not provided to FDA until after Chiron's license suspension. The MHRA, however, was provided with Chiron's findings on September 24, 2004. As a result, MHRA concluded its final investigative visit to Chiron on September 30, 2004. The FDA has since reviewed the report and instructed committee staff that had the agency received the draft report sooner, the Chiron facility would have been reinspected, whether or not MHRA suspended Chiron's manufacturing license.

FDA, MHRA, and Chiron all agree that Chiron's license suspension resulted from systematic problems within Chiron's Liverpool facility, based on a lack of manufacturing oversight and execution.

In addition, all parties agree that prior inspections conducted by both FDA and MHRA at the Chiron facility did not foreshadow the license suspension. While some issues at the facility continued from 2003 until September 2004, Chiron's license suspension wasn't based on contamination in flu vaccine lots or other issues that were addressed in previous inspections. It would be inappropriate to imply that problems at the Chiron facility in 2003 recurred in 2004 and contributed to the closure of the facility.

Questions have been asked as to why FDA was kept in the dark regarding Chiron's license suspension until October 5th. Pursuant to the U.K.'s Medicines Act, MHRA is prohibited from sharing commercial information without the consent of the manufacturer involved. FDA, MHRA, and Chiron all informed committee staff that it is widely accepted and understood that the two agencies do not discuss their own actions with regard to companies over which they each have jurisdiction. In addition, it would be standard procedure for Chiron not to discuss this interaction with FDA or MHRA with the other agency. Since October 5th, Chiron has permitted FDA and MHRA to communicate on all issues.

This investigation has been conducted in a bipartisan manner. Politics has no place in the public health arena. I hope that this spirit of cooperation isn't threatened today by those who choose to ignore standard FDA protocol, accepted by vaccine manufacturers worldwide, and place the sole blame for the flu vaccine shortage on a single agency, rather than taking an objective look at all of the facts presented during the committee's investigation. If protocols need to be tweaked, however, then let us talk about tweaking them.

After all, should FDA be held accountable for decisions made by Chiron without its knowledge or for actions taken by MHRA that were legally protected by the law of the U.K.? If the committee spends too much time placing blame and pointing fingers, we will be unable to look to the future to ensure that the United States has an adequate flu vaccine supply. Let's let experience be our teacher.

My main goals in this investigation are to understand the lessons learned from the events leading up to and occurring since October 5, 2004, and, most importantly, to work vigilantly with U.S. health officials and private industry to ensure that a similar situation does not occur in the future.

Based on my findings with the FDA, MHRA, and Chiron, I am optimistic that Chiron will be able to produce vaccine for next year's flu season. The license suspension didn't prohibit Chiron from procuring its startup materials for next year. As of today, Chiron has contracted and paid for its egg supply for the 2005–2006 flu season. MHRA is extremely pleased with the remediation plan that Chiron has submitted, and a followup inspection will be conducted in late December to evaluate Chiron's progress.

It is important to recognize there is a need to expand the current number of FDA approved flu vaccine manufacturers and to bring those manufacturers into the U.S. markets. We are going to work on legislation designed to provide incentives to flu vaccine manufacturers in hopes that we can stimulate the vaccine market domestically.

Since our October 8, 2004 hearing, both Aventis Pasteur and MedImmune have been able to produce additional doses of flu vaccine. FDA has also identified and negotiated for approximately 5 million doses of flu vaccine from foreign manufacturers. Additionally, the Nation has a supply of enough antiviral medicines to treat about 40 million people. These antiviral drugs can be used to prevent or treat the flu if symptoms are identified early.

Our witnesses today will discuss how U.S. health officials are procuring and adequately distributing the flu vaccine to the high-risk population and preparing for next year's flu season, and what incentives can be provided to manufacturers to ensure a stable annual flu vaccine supply.

In addition, I am pleased that Howard Pien, the president of Chiron Corp., is present to speak publicly for the first time since October 5, 2004. I know we are anxious to hear his testimony as to Chiron's remediation plan and how Chiron is moving forward in preparation for next year's flu season.

We have an excellent roster of witnesses, and I would like to thank all of them for appearing before the committee, and look forward to their testimony.

[The prepared statement of Chairman Tom Davis follows:]

Statement of Chairman Tom Davis
Committee on Government Reform Hearing
"The Nation's Flu Shot Shortage: Where are We Today and How Prepared are We for Tomorrow?"
November 17, 2004

Good afternoon, a quorum being present, the Committee on Government Reform will come to order. I want to welcome everyone to today's hearing, the Committee's second oversight hearing in six weeks on this year's U.S. influenza vaccine supply.

As most are now aware, on October 5, 2004, the Medicines and Healthcare Products Regulatory Agency, the United Kingdom's version of the U.S. Food and Drug Administration, suspended Chiron Corporation's manufacturer's license for a period of three months. Chiron planned on delivering 46-48 million doses of flu vaccine, almost half of the U.S. supply.

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This investigation has been conducted in a bipartisan manner. Politics has no place in the public health arena. I hope this spirit of cooperation is not threatened today by those who choose to ignore standard FDA protocol, accepted by vaccine manufacturers worldwide, and place the sole blame on for the U.S. flu vaccine shortage on a single Agency, rather than taking an objective look at all the facts presented during the Committee's investigation. If protocols need to be tweaked, then let's talk about tweaking them.

After all, should FDA be held accountable for decisions made by Chiron without its knowledge or for actions taken by MHRA that were legally protected by law of the U.K.? If the Committee spends too much time placing blame and pointing fingers, we will be unable to look to the future to ensure the U.S. has an adequate flu vaccine supply. Let's let experience be our teacher.

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We have an excellent roster of witnesses today and I would like to thank all of them for appearing before the Committee and I look forward to their testimony.

Chairman TOM DAVIS. I would now like to yield to Mr. Waxman for an opening statement.

Mr. WAXMAN. Thank you, Chairman Davis, for holding this hearing on the flu vaccine shortage. You and I share the goal of establishing a healthy vaccine supply in the United States, and effective government oversight is an important part of this process.

This year's flu vaccine crisis raises three important oversight questions.

The first question is how the United States came to depend on just two companies for the flu vaccine. The Institute of Medicine, the Government Accountability Office, the National Vaccine Advisory Committee have all issued reports exposing the weakness of our national vaccine infrastructure, and we can't afford to ignore their recommendations any longer. And they have been making recommendations since the year 2001.

The second question is why the vaccine shortage led to such confusion and chaos. In a series of reports over the last 4 years, GAO repeatedly warned that the United States does not have a plan to ensure that the highest risk people are immunized in the event of a shortage. The seniors who have been standing in lines for hours trying to get a flu vaccine know that GAO was right.

And the third question is the primary subject of today's hearing: Did FDA do its job to protect the U.S. vaccine supply?

Since the vaccine shortage began, senior administration officials, including Acting FDA Commissioner Lester Crawford, have been reassuring the public that the FDA made no mistakes and did everything possible to protect the vaccine supply.

Today we will evaluate those claims.

On October 13th, Chairman Davis and I asked FDA to provide copies of documents relating to its oversight of the Chiron vaccine plant in Liverpool, England. This is the plant that British regulators shut down on October 5, causing the United States to lose approximately half of its supply of the flu vaccine.

We have now received and reviewed over 1,000 pages of documents. We have also met with FDA officials, and the chairman traveled to England with majority and minority staff to interview British and Chiron officials.

The documents show that FDA failed to provide effective oversight. Expert scientists at FDA knew about serious problems at the Liverpool facility in June 2003, but there was not sufficient leadership at the agency to ensure that they were fixed.

My staff prepared a background memorandum for this hearing that describes the documents and their significance in detail, and I ask that this memorandum and the redacted versions of documents cited in the memorandum be made part of the hearing record.

Chairman DAVIS. No objection. Let me just add that I think that all records in the binders before the Members, majority and minority, ought to be made part of the record, and if there is no objection, so ordered.

[The information referred to follows:]

To:	Democratic Members of the Government Reform Committee
From:	Ranking Minority Member Henry A. Waxman
Re:	Summary of FDA Documents
Date:	November 17, 2004

On November 4, in response to a request from Chairman Davis and Rep. Waxman, the Food and Drug Administration provided to the Committee more than 1,000 pages of documents relating to FDA's oversight of the Chiron flu vaccine manufacturing facility in Liverpool, England. This is the facility that British regulators shut down on October 5 due to contamination problems, causing the United States to lose approximately half of its supply of flu vaccine.

To assist members in their preparation for the Committee's flu hearing on November 17, 2004, this memorandum reviews the key documents provided by FDA to the Committee.

Executive Summary

The new documents raise serious questions about the adequacy of FDA's oversight. They reveal that despite being aware of major problems at the vaccine manufacturing facility as early as June 2003, FDA missed repeated opportunities to correct them. Specifically, the documents show:

- **FDA found serious and widespread problems at the facility in June 2003.** FDA found problems in 20 areas of vaccine manufacture and distribution, including high levels of bacterial contamination, poor sanitary practices, and inadequate remedial efforts.

- **Problems identified during the June 2003 inspection recurred in 2004 and contributed to the closure of the facility.** The June 2003 inspection identified as significant problems elevated levels of "bioburden" in vaccine pools, contamination by *Serratia* bacteria, deficiencies in the plant's "aseptic connections," improper sanitary practices, and inadequate efforts to investigate and eliminate sources of contamination. These problems recurred in 2004 and were among the factors identified by British, Chiron, and FDA investigators as contributing to the shutdown of the facility. For example, FDA's October 15, 2004, inspection, which confirmed that none of the Chiron

vaccine was safe for U.S. use, cited bioburden problems at the facility that were "not corrected from previous inspection of 2003."

- **FDA officials "downgraded" the agency's response to the June 2003 inspection from "official action indicated" to "voluntary action indicated."** The FDA team that conducted the June 2003 inspection recommended that the agency pursue official enforcement action against the Liverpool facility. But their recommendation that FDA initiate enforcement action was rejected. Instead, FDA requested only voluntary action by the company.

- **FDA delayed sending the final inspection report to the company until June 2004.** When FDA requests voluntary remedial action by a manufacturer, FDA is supposed to send the manufacturer the full inspection report to help the manufacturer understand what corrective actions are needed. In the case of the Chiron facility, FDA did not send the final inspection report to Chiron until June 2004, a year after the inspection occurred and nine months after it was supposed to have been sent. At this point, manufacture of the 2004 vaccine supply was already well underway.

- **FDA never reinspected the plant after June 2003 to determine whether the problems were resolved.** In September 2003, FDA informed the company in writing that the agency would assess the company's corrective actions at its next inspection. This inspection was not scheduled until after the facility was shut down on October 5, 2004, by which time it was too late to save the U.S. flu vaccine supply.

- **FDA remained passive when evidence of actual contamination came to light in August 2004.** After Chiron notified FDA on August 25, 2004, that millions of doses of flu vaccine were contaminated, FDA officials relied on weekly conference calls with Chiron, rather than independent inspections, to monitor the company's progress. These calls included discussion of how FDA officials could dispel fears of a vaccine shortage. By contrast, British regulators launched a series of actions commencing two weeks after receiving the notice from Chiron. These included sending a team of regulators to the facility twice (from September 13 to 15 and from September 28 to 30), reviewing the company's records and draft investigation report, convening two high-level committees, and ultimately suspending the facility's license. FDA officials never asked Chiron or the British regulators about the British activities, and the British regulators were barred by law from informing FDA of their findings absent consent from Chiron.

The Committee staff met with FDA officials on November 15 to discuss the FDA documents. The FDA officials at the meeting, including John Taylor, the Associate Commissioner for Regulatory Affairs, acknowledged that the problems identified during the June 2003 inspection were "relevant" to the contamination in finished lots of vaccine and other systemic concerns that led to the closure of the Chiron plant in October 2004. They also maintained that other factors, such as an increase in the facility's output, played a significant role. The FDA officials justified FDA's failure to take official enforcement action against the facility in June 2003 on the grounds that conditions in the facility appeared to be improving, rather than deteriorating.

The June 2003 Inspection

FDA regulations require that the agency inspect vaccine manufacturers, whether foreign or domestic, at least once every two years.[1] In June 2003, FDA inspected the Liverpool flu vaccine plant of the PowderJect Corporation, which was in the process of being acquired by Chiron.[2] Referring to this inspection, Acting FDA Commissioner Lester Crawford said, "what happened in 2003 has no relevancy for 2004."[3]

In fact, many of the problems detected by FDA during the June 2003 inspection reappeared in 2004 and were among the factors cited as likely or potential causes of the vaccine contamination that led to the closing of the facility this year.

FDA's June 2003 inspection findings are contained in two documents: (1) the Form 483, which is a list of areas of concern that is produced by the FDA inspector during the inspection and is left with the company at the close of the inspection; and (2) the Establishment Inspection Report, which is a detailed description of the findings of the FDA inspection. FDA provided both of these documents to the Committee.

The inspection forms indicate that FDA inspectors found serious problems in 20 areas of vaccine manufacturing and distribution.[4] Several of the problems directly related to the risk of bacterial contamination.

First, the FDA inspectors found high levels of overall bacterial contamination (called "bioburden") in several lots of vaccine after a key step called "ultrafiltration," which is a point in the production process that is supposed to remove the vast majority of bacteria.[5] In some cases, the FDA inspectors found records of bacteria concentrations that were more than a thousand

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[1]21 CFR 600.21.

[2]PowderJect was formally incorporated into Chiron on October 31, 2003. In purchasing PowderJect, Chiron assumed responsibility for its license to manufacture flu vaccine and its interactions with FDA. Chiron Vaccines, *Chiron Vaccines Expands Presence in UK Following Integration of PowderJect Pharmaceuticals* (Oct. 31, 2003) (online at http://www.powderject.com/company/vaccines_Press_Area_31_October_2003.php).

[3]*Tommy Thompson Holds a News Conference Regarding the Flu*, FDCH Political Transcripts (Oct. 21, 2004).

[4]U.S. Food and Drug Administration, *Inspectional Observations, Form 483, Evans Vaccines Ltd.* (June 10, 2003); U.S. Food and Drug Administration, *Establishment Inspection Report, Evans Vaccines Ltd.* (2003) (hereinafter "Establishment Inspection Report").

[5]Establishment Inspection Report at 13.

times higher than expected.[6] FDA also found evidence of contamination after sterile filtration, the point beyond which there should not be any bacterial growth.[7]

Second, the FDA inspectors found unexpected contamination with potentially lethal bacteria after ultrafiltration. The inspectors determined that on 14 occasions between March 2001 and July 2002, the company found *Serratia* bacteria present in vaccine pools.[8] *Serratia* contamination is a serious problem, because the bacteria can cause abscesses, sepsis, and even death if injected in the human body.

Third, the FDA inspectors identified poor sanitary practices that increased the risk that bacteria could contaminate sterile parts of the production process. For example, the inspectors noted that "curtains" that were supposed to segregate sterile areas of the plant from nonsterile areas were not properly maintained. The inspectors reported:

> [D]uring the June 6th 2003 walk through of the firm's facility it was noted that there was no documentation in the batch record regarding missed stoppers or seals and there is no procedural requirement to do so. Also, a panel about 8 by 10 inches was open in the cabinet under the filling machine and there was no information on the length of time that this condition had existed or that repairs had been scheduled. Furthermore, an operator was noted to be pushing curtains into the area near open empty vials while retrieving tipping vials on 2 occasions disrupting vertical laminar flow and 2 plastic yellow beakers used for holding forceps were observed scratched and yellowed.[9]

One of the most serious problems identified during the June 2003 inspection was that the company did not appropriately investigate and correct possible sources of contamination. For example, the agency learned that the company identified a susceptibility to contamination in the system of connections (called "aseptic connections") between tanks of vaccine in the "Formulation area" of the plant.[10] Yet the FDA inspectors found that the company did not take the appropriate steps to respond to this portal for bacterial contamination. FDA determined that the company's "corrective actions are incomplete."[11]

Similarly, regarding the elevated "bioburden," the inspectors wrote, "there was no documentation that the firm opened a formal investigation into the high levels of bioburden

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[6] *Id.*

[7] Establishment Inspection Report at 15.

[8] FDA also found that 14 vaccine pools had been contaminated by *Klebsiella* bacteria and "several additional batches" by *Enterobacter*. Establishment Inspection Report at 15–16.

[9] *Id.* at 2.

[10] Establishment Inspection Report at 14.

[11] *Id.*

levels to find the root cause and eliminate the potential source/sources of the contamination."[12] The company had also failed to conduct adequate investigations into vaccine sterility and stability issues.[13]

The 2003 inspection also reported that the company sold re-filtered vaccine in the 2001-2002 season without notifying FDA as required by law. Company employees initially told FDA that the re-filtered vaccine was not shipped to the United States. Then the company said that FDA had granted approval to sell re-filtered vaccine. In fact, inspectors determined that neither story was true.[14]

Contrary to Acting Commissioner Crawford's assertion that what happened in 2003 had "no relevancy" to the current flu vaccine shortage, many of the problems that led to the shutdown of the Chiron facility last month were foreshadowed by the June 2003 inspection:

- This year's problems began when Chiron found that several million doses of vaccine had been contaminated with the bacteria *Serratia*.[15] This is the same organism that the FDA inspectors identified as a recurring contamination problem, at an earlier stage in production, in June 2003.[16]

- When British regulators investigated the 2004 *Serratia* contamination, they discovered several months of abnormally high levels of bioburden in vaccine pools and determined that the company had failed to understand what was causing these high levels.[17] These concerns were similar to those identified by the FDA inspectors in June 2003.[18] When FDA investigators finally visited the plant in October 2004, they found that bioburden problems were "not corrected from previous inspection of 2003 in that similar occurrences noted during this inspection."[19]

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[12]Establishment Inspection Report at 2.

[13]Establishment Inspection Report at 12 and 14.

[14]Establishment Inspection Report at 9–10.

[15]*Half of U.S. Flu Vaccine Withheld,* Washington Post (Oct. 6, 2004) ("In August, Chiron told that agency it had found some lots of vaccine contaminated with *Serratia*, a genus of 'gram-negative' bacteria that can cause severe, and occasionally fatal, infections in human beings").

[16]Establishment Inspection Report at 16.

[17]Medicines and Healthcare Products Regulatory Agency, *2004 Fluvirin Manufacturing Campaign — Inspectorate Findings* (Oct. 4, 2004).

[18]Establishment Inspection Report at 13.

[19]U.S. Food and Drug Administration, *Inspectional Observations, Form 483, Evans Vaccines, an Affiliate of Chiron Corporation*, 6 (Oct. 15, 2004).

- When Chiron investigated the August 2004 *Serratia* contamination, the company determined that the bacteria could have entered the vaccine through aseptic connections between tanks in the formulation area of the plant.[20] An FDA official also wrote in an internal agency memo that the Serratia contamination was most likely to have occurred through these connections between tanks involved in formulation.[21] This is same part of the production process that the FDA inspectors reported had not been adequately investigated and corrected in June 2003.[22]

- In reviewing possible sources of the 2004 *Serratia* contamination, Chiron found damage to the flooring, a skipped monthly cleaning in June 2004, and an employee whose training in aseptic technique had lapsed. While Chiron did not consider any of these specific problems to be the cause of this year's vaccine problems, the company considered it probable that bacteria had inadvertently been passed from nonsterile areas to sterile areas of the production process.[23] In October 2004, FDA inspectors again identified problems in the handling of curtains separating sterile from nonsterile areas and other sanitary practices at the plant.[24] FDA inspectors had expressed concern about the consequences of such problems in June 2003.[25]

- FDA and British regulators concluded in October 2004 that Chiron had failed to investigate the contamination problems effectively.[26] Difficulty pursuing such investigations was a recurring theme of the June 2003 inspection.[27]

The FDA officials who briefed the Committee on November 15 were asked whether the problems identified during the June 2003 inspection were related to the problems that led to the closure of the facility in October 2004. They acknowledged that a number of the problems found during the June 2003 inspection were the same as or related to problems found in 2004. They emphasized, however, that the problems found in 2004 were worse and more widespread than in

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[20]Chiron Vaccines, *Fluvirin Sterility Investigation*, 39–46 and 66–67 (2004).

[21]Angela K. Shen, U.S. Food and Drug Administration, *Status of 2004 Flu Campaign* (Sept. 2, 2004).

[22]Establishment Inspection Report at 14.

[23]Chiron Vaccines, *supra* note 20, at 39–46.

[24]U.S. Food and Drug Administration, *supra* note 19.

[25]Establishment Inspection Report at 24–25.

[26]Medicines and Healthcare Products Regulatory Agency, *supra* note 17; U.S. Food and Drug Administration, *supra* note 19.

[27]U.S. Food and Drug Administration, *Inspectional Observations, Form 483, Evans Vaccines Ltd.* (June 10, 2003).

2003. In their view, the effort to increase the output of the Chiron plant in 2004 contributed significantly to the deterioration in the conditions.[28]

FDA's Response to the June 2003 Inspection

The June 2003 inspection report and Form 483 could have served as a road map for stringent enforcement and oversight on FDA's part. However, the agency missed opportunities to ensure that the problems would be fixed and the public would be protected.

In a previous inspection in 1999, FDA inspectors identified problems at the Liverpool facility. The inspectors responded to these problems by issuing an FDA "warning letter."[29] This is an official enforcement action that is released to the public. If the manufacturer does not remedy the violations identified in the warning letter, FDA can initiate legal action against the manufacturer. In addition, a warning letter generally ensures that another inspection will be conducted to assess whether compliance has been achieved.

After the June 2003 inspection, however, FDA failed to initiate any official enforcement action. Although FDA inspectors recommended official enforcement action, this recommendation was rejected. The October 5 handwritten notes of John Eltermann, the director of the Division of Manufacturing and Product Quality in FDA's Center for Biologics, Evaluation and Research under the heading of June 2003 state: "TBio – OAI → VAI." There is a single word underneath: "downgraded."[30]

FDA officials were asked about the significance of these notes at the November 15 briefing. The FDA officials explained that the abbreviation "TBio" refers to "team biologics," the FDA unit responsible for inspecting vaccine manufacturers, the abbreviation "OAI" refers to "official action indicated," and the abbreviation "VAI" refers to "voluntary action indicated." According to the FDA officials, the "team biologics" inspectors, who conducted the June 2003 inspection, recommended that the agency pursue official enforcement action against the Liverpool facility. But this recommendation was not accepted. Instead, it was "downgraded" to a request for voluntary action by the company, which carries no legal weight.[31]

According to the FDA officials, the decision to "downgrade" the enforcement action was primarily justified by the quality of the company's plan to fix the problems and by improvement in bacterial contamination noted during the 2002 to 2003 flu season. The June 2003 inspection

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[28]U.S. Food and Drug Administration, Briefing for Government Reform Committee staff (Nov. 15, 2004).

[29]Warning letter from Steven A. Masiello, Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, to Mr. John E. O'Brian, Head of Primary Production, Medeva Pharma Ltd. (Oct. 21, 1999).

[30]John Eltermann, U.S. Food and Drug Administration, *Notes of Internal FDA Discussions* (Oct. 5, 2004).

[31]U.S. Food and Drug Administration, *supra* note 28.

report found 20 deficiencies at the plant compared to 31 in the 2001 inspection. According to the 2003 inspection report, 26 of the problems identified in the 2001 inspection had been corrected. Five deficiencies remained uncorrected.[32]

Acting FDA Commissioner Crawford has assured the public that the agency did provide adequate oversight of the vaccine facility after the June 2003 inspection. Responding to a question about whether Chiron had implemented necessary corrective actions after the June 2003 inspection, Dr. Crawford stated: "We monitored those actions. Those actions were taken."[33]

In fact, the documents indicate otherwise. During the 16 months between the June 2003 inspection and the October 2004 shutdown of the facility, FDA failed to inspect — even once — whether the manufacturing defects it identified in June 2003 had been fixed. FDA informed the company that "corrective actions will be reviewed and assessed during the next inspection."[34] But such an inspection did not occur until mid-October 2004, after British regulators had shut down the facility. By then, it was too late to prevent the flu vaccine shortage.[35]

FDA also failed to respond to the company's requests for assistance. On June 27, 2003, the plant's manager wrote to FDA that the company "would like to meet with the agency as soon as possible" to review its response plan. He stated, "At this meeting we would welcome the opportunity to present to the agency our Quality Systems Improvements Program."[36] FDA replied to Chiron over two months later, on September 3, 2003. The response states that the company's letter would be placed in its "permanent file."[37] No mention was made of the meeting request, and according to Chiron officials, no meeting ever occurred.[38] When asked during the November 15 congressional briefing about the failure of FDA to meet with Chiron, the FDA officials stated that the agency often declines to meet with companies that have presented adequate plans for addressing inspection problems.[39]

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[32]Establishment Inspection Report at 5–6.

[33]*Tommy Thompson Holds a News Conference Regarding the Flu*, *supra* note 3.

[34]Letter from Philip R. Lindeman, Compliance Officer, U.S. Food and Drug Administration, to Mr. Andy Sneddon, Site Manager, Evans Vaccines, Ltd. (Sept. 3, 2003).

[35]U.S. Food and Drug Administration, *FDA Team Completes Inspection of Chiron's Liverpool Flu Vaccine Plant* (Oct. 15, 2004) (online at http://www.fda.gov/bbs/topics/news/2004/NEW01125.html).

[36]Letter from Mr. A.H. Sneddon, Site Director, Evans Vaccines, Ltd., to K. Midthun, Center for Biologics Evaluation & Research, U.S. Food and Drug Administration (Jun. 27, 2003).

[37]Letter from Philip R. Lindeman, *supra* note 34.

[38]Chiron Corporation, Briefing for Chairman Davis and Government Reform Committee staff (Nov. 11, 2004).

[39]U.S. Food and Drug Administration, *supra* note 28.

One problem acknowledged by the FDA officials at the November 15 briefing was the long delay in providing the final inspection report to Chiron. On June 7, 2004 — a year after the completion of the June 2003 inspection — Chiron officials wrote FDA to request a copy of the Establishment Inspection Report from the June 2003 visit.[40] This report contains many more details and recommendations than the Form 483. According to FDA staff, this report should have been sent to the facility in September 2003, when the decision was made to request only voluntary action, in order to assist the plant in taking the appropriate remedial steps. In fact, the report was not provided until after FDA received Chiron's June 7, 2004, request, well after the start of vaccine manufacturing for the 2004 to 2005 season.[41] According to FDA officials, confusion between FDA's Center on Biologics, Evaluation and Research and the Office of Regulatory Affairs was responsible for the delay.[42]

FDA's Response to the August 2004 Contamination

FDA had another opportunity to intervene in August 2004, when Chiron reported that it had detected contaminated vaccine at the Liverpool facility. On August 26, 2004, Chiron announced that eight lots of vaccine, representing several million doses, had been contaminated by *Serratia*.[43] The documents indicate, however, that FDA failed to act decisively.

Acting Commissioner Crawford has characterized the British and FDA inspections in response to the August announcement as "about the same thing" and said that the two countries' drug agencies were "in synchrony."[44] But the documents do not support these assertions. Even though none of the vaccine contaminated in August was intended for the British market, and even though the United Kingdom relied on the Chiron plant for a small fraction of its overall flu vaccine supply, British regulators did far more than their FDA counterparts to ensure the safety of the flu vaccine.

When Chiron notified FDA of the *Serratia* contamination on August 25, an agency inspector coincidentally was present at the facility conducting a limited inspection of a new filling line for vaccine. Chiron asked to brief this inspector about the company's investigation into the problem. According to his notes, this inspector learned basic details about the

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[40]Letter from Peter McBride, Regulatory Affairs Managers at Evans Vaccine Limited (part of Chiron Vaccines) to Dr. James S. Cohen, Office of Compliance and Biologics Quality, Food and Drug Administration (Jun. 7, 2004).

[41]U.S. Food and Drug Administration, *supra* note 28.

[42]U.S. Food and Drug Administration, *supra* note 28.

[43]Chiron Corporation, *Chiron Delays Fluvirin(R) Influenza Virus Vaccine Shipments* (Aug. 26, 2004) (online at http://www.chiron.com/media/pressreleases/index.html).

[44]*Tommy Thompson Holds a News Conference Regarding the Flu*, *supra* note 3.

contamination of eight lots of the vaccine and heard of the company's plans to "continue to identify root cause."[45]

From this point on, however, FDA relied on conference calls with the company — not its own inspections or review of company records — to monitor the company's progress.

According to internal agency notes and e-mails, these conference calls would include an update from Chiron on the company's findings, combined with a discussion about how to handle the public relations problems created by the August announcement. On September 9, for example, FDA and Chiron discussed the media coverage of the *Serratia* contamination and considered a plan to "dispel fears of shortages, and to state that, overall, more vaccine is expected to be available this season than last year."[46]

Even when asked by the company for more active oversight of the *Serratia* investigation, FDA remained passive. On September 20, a senior Chiron official asked whether the agency had any "special issues" for the company to act upon before going forward. In response, an FDA official said that he did not think so, "provided they are following SOPs [standard operating procedures], the product meets specifications and they believe that they have isolated and resolved the issue."[47]

Internal e-mails indicate that even in late September, FDA employees tried to dispel rumors of a pending shortage. For example, FDA officials spoke on September 20 with a senior official at the National Vaccine Program Office of the Department of Health and Human Services to alleviate heightened concerns about the Chiron situation.[48]

By contrast, upon learning of *Serratia* contamination, Britain's Medicine and Healthcare products Regulatory Agency (MHRA) — the British equivalent of FDA — took a different approach. Within two weeks, the agency sent a team of inspectors to the facility to conduct a two-day "fact finding" visit to the plant on September 13 and 14, 2004.[49] Reviewing the company's records, the British inspectors found that Chiron knew of potential contamination

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[45]U.S. Food and Drug Administration Inspector David Cho, *Notes from Discussion with Chiron/Evans on 25 August 2004* (Aug. 25, 2004).

[46]E-mail communication from Elaine Cole, U.S. Food and Drug Administration, to other FDA employees, *Conference Call Summary — Chiron's Fluvirin* (Sept. 9, 2004).

[47]E-mail communication from Roland A. Levandowski, U.S. Food and Drug Administration, to other FDA employees, *Evans/Chiron Update* (Sept. 20, 2004).

[48]E-mail communication from Roland A. Levandowski, U.S. Food and Drug Administration, to other FDA employees, *RE: Evans/Chiron Update* (Sept. 20, 2004).

[49]Medicines and Healthcare Products Regulatory Agency, *Briefing Note: Chiron Vaccines, Speke, Liverpool, Influenza Vaccine*, 1 (Oct. 5, 2004).

problems as early as April 2004.[50] They also learned that sterility failures occurred in July 2004.[51]

On September 15, MHRA convened the Cross-Agency Vaccine Group to review the inspectors' report.[52] This high-level panel advised that a second visit should take place after a review of the company's draft internal investigation of the *Serratia* contamination.[53]

This draft was provided by Chiron on September 24. It was immediately reviewed by senior British regulators, including the Acting Director of MHRA's Inspection and Enforcement Division.[54] While FDA officials never received this draft report from the company, the British officials quickly determined that the report "had not addressed the root causes of the contamination problems."[55]

In response, the British arranged for a second "for cause" inspection to take place from September 28 to 30.[56] MHRA also requested, in writing, that Chiron not release "any batches of vaccine to any market pending that visit."[57]

After the inspection from September 28 to 30, MHRA's Cross-Agency Vaccine Group met again on October 1. At this meeting, inspectors identified 19 "serious issues related to microbial contamination and potential for microbial contamination in influenza vaccine production."[58] According to the inspectors, "these constituted a critical situation regarding sterility assurance of the production process, leading to potential and actual microbial contamination of the finished product by a pathogenic organism."[59]

The Cross-Agency Vaccine Group referred the report to MHRA's Inspection Action Group, which recommends licensing actions.[60] This panel met on October 4 and recommended

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[50] *Id.*

[51] *Id.*

[52] *Id.*

[53] *Id.*

[54] *Id.*

[55] *Id.*

[56] *Id.*

[57] *Id.*

[58] *Id.* at 2.

[59] *Id.*

[60] *Id.*

the suspension of Chiron's license to prevent "a potentially serious risk to patients through the administration of a vaccine that may be contaminated."[61] The closure of the Chiron facility by the British was announced the following day, on October 5.

FDA officials were caught completely unaware by these British actions. In fact, FDA officials did not even know that British regulators were investigating the Chiron facility until October 5, after the facility was shut down. At the November 15 briefing, FDA officials acknowledged that FDA never asked Chiron or the British regulators about the activities of the MHRA.[62] For their part, the British regulators did not tell FDA officials about their efforts because they were prevented by law from telling FDA of their activities without the consent of Chiron.

After MHRA's public announcement of the plant's shutdown on October 5, FDA finally conducted an on-site inspection of the Chiron facility which ended on October 15. This inspection confirmed that "none of the influenza vaccine manufactured by the Chiron Corporation for the U.S. market is safe for use."[63]

At the November 15 briefing, FDA officials stated that the agency was planning to review the company's inspection report during the week of October 5. According to these officials, FDA would have immediately recognized the deficiencies in the Chiron report and scheduled a rapid inspection. Yet even if FDA had acted immediately, the earliest that FDA could have suspended the company's license would have been after the October 15 inspection. During this delay, additional millions of flu shots from the other manufacturer serving the U.S. market might have been administered to low-risk individuals around the country, worsening the shortage to come.

After the License Suspension

After British regulators suspended Chiron's license to manufacture and market flu vaccine on October 5, 2004, FDA was unclear on how to proceed. Letters from the Office of the General Counsel at FDA to MHRA indicate that the agency did not understand the reach or implications of the British decision. An e-mail to MHRA from the associate chief counsel for biologics asked "for a copy of the law or regulation which provides the licensing authority in the United Kingdom with the power to order the suspension."[64] FDA also asked to learn whether Chiron had any remedies for the administrative action, whether the company could ask for retesting of batches or lots, and whether the suspension order affected lots located in the United States.[65]

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[61] *Id.*

[62] U.S. Food and Drug Administration, *supra* note 28.

[63] U.S. Food and Drug Administration, *supra* note 35.

[64] E-mail communication from Office of General Counsel, U.S. Food and Drug Administration, to MHRA, *Questions Regarding the Suspension* (Oct. 6, 2004).

[65] *Id.*

Conclusion

In sum, the documents from FDA disclose that the agency failed to provide effective oversight of the Liverpool facility. Despite identifying serious problems at the facility in June 2003, FDA failed to take official enforcement action or to conduct followup inspections. Even after being told in August 2004 of additional contamination, FDA did little to determine the true scope of the problems. If FDA had acted differently — by issuing an official warning letter, reinspecting the facility, and responding aggressively to the August 2004 contamination — the flu vaccine shortage might have been avoided or mitigated.

To: Chairman Davis and Committee on Government Reform Majority Members
From: Committee on Government Reform Majority Staff
RE: Response to Minority's Summary of FDA Documents
Date: November 17, 2004

Last week, Chairman Davis, Majority and Minority staff traveled to London. The CODEL was scheduled pursuant to the Committee's investigation into the October 5, 2004 Chiron manufacturing license suspension and the resulting U.S. flu vaccine shortage. The CODEL met with the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) and Chiron. After returning from London, a Committee meeting was held with U.S. Food and Drug Administration (FDA) to review documents obtained by the Chairman and Mr. Waxman as a result of the investigation and the information obtained while on the CODEL.

Today Mr. Waxman will distribute a 13-page memo to the Committee's Minority Members titled "Summary of FDA Documents." The memo is extremely misleading. FDA documents are taken out of context. Explanations provided to the Committee as to documents written and actions taken by MHRA, FDA, and Chiron are ignored by the Minority. The Minority has chosen to ignore standard FDA protocol, accepted by vaccine manufactures worldwide. The Minority's memo places the sole blame for the U.S. flu vaccine shortage on FDA, yet another partisan attack on the Administration, rather than taking an objective look at all the facts presented during the Committee's investigation.

Response to Minority's Memo

FDA standard protocol is to inspect overseas manufacturing facilities every two years. FDA conducted a standard inspection of Chiron's Fluvirin facility in June 2003. Upon being notified of Chiron's license suspension on October 5, 2004, FDA conducted another, not previously scheduled, inspection of the Fluvirin facility.

After an inspection, FDA provides the manufacturer with a Form 483. The Form 483 lists FDA's findings and provides a framework for the manufacturer to take corrective measures based on FDA's findings. FDA provided the Committee with the Form 483 from its June 2003 and October 2004 inspections.

A Form 483 is highly technical and scientific. It would be highly difficult for an individual without a graduate degree in science and familiarity with FDA protocol to interpret a Form 483. The Minority's superficial conclusions reflect this point. The Minority has chosen to pick and choose particular sentences from a detailed 7-page findings of FDA's June 2003 Form 483 to draw a causal connection between the FDA's findings in 2003 with Chiron's license suspension. In particular, the Minority cites that the June 2003 Form 483 refers to elevated levels of "bioburden" in vaccine pools, contamination by *Serratia* bacteria, deficiencies in the plant's "asceptic connections," improper sanitary practices, and inadequate efforts to investigate and correct sources of contamination at the Fluvirin facility. Because the Minority identified the same words

contained in FDA's 10-page October 2004 Form 483, they find it appropriate to imply that "widespread problems at the facility in June 2003 . . . recurred in 2004 and contributed to the closure of the facility."

In fact, this connection between the findings of the June 2003 inspection and Chiron's license suspension has been disputed by MHRA, FDA, and Chiron. In each meeting, it was explained that while FDA may have found similarities in the condition of the Fluvirin facility in June 2003 and October 2004, **the cause of Chiron's license suspension was a direct result of systemic problems within the facility, based upon a lack of manufacturing oversight and execution. In fact, Chiron's license was not suspended based upon contamination in flu vaccine lots or issues addressed subsequent to the June 2003 inspection.**

The Minority continues to mislead Committee Members regarding Chiron's June 2003 inspection with its analysis of a handwritten note by John Eltermann, Director of the Division of Manufacturing and Product Quality in FDA's Center for Biologics, Evaluation and Research. In the note, Mr. Eltermann has written "Tbio – OAI → VAI downgraded." "Tbio" stands for "team biologics," the FDA officials who conduct inspections of vaccine manufacturing facilities. "OAI" stands for "official action indicated," and "VAI" stands for "voluntary action indicated." Standard protocol for a team biologics is to recommend an FDA response to an inspection. The team biologics then meets with officials from FDA to discuss its recommendation and make a final decision. FDA told the Committee that the team biologics initially recommended an official action after Chiron's June 2003 inspection, but upon further discussion and a review of Chiron's written response to the June 2003 Form 483, it was agreed by all parties within FDA to issue a voluntary action.

The Minority chose to frame this process as FDA officials "rejected" the team biologics recommendation. However, as the Committee learned from FDA, it is not uncommon for the team biologics to make one recommendation and upon further discussion, alter its recommendation. The team biologics participates fully in the decision making process. It is irresponsible to suggest that a collaborative professional decision made by FDA officials and inspectors is a causal connection to lack of oversight by FDA and ultimately led to Chiron's license suspension.

The Minority informs its Members that FDA never reinspected the Chiron Fluvirin facility after the June 2003 inspection to determine if existing problems were resolved. This lack of inspection contributed to Chrion's license suspension. Again, this attempt at creating a causal connection between FDA's actions and Chiron's license suspension is not only irresponsible, but grossly misleads Members as to standard FDA procedures.

FDA inspects foreign facilities once every two years. A manufacturer is provided with a Form 483 at the conclusion of the inspection. The manufacturer then responds to the Form 483. This response includes the manufacturer's plans to remedy the issues highlighted by FDA as weaknesses in the Form 483. If FDA reviews and accepts the

manufacturer's response, the file is considered closed. FDA will then conduct another inspection within two years and will assess whether the manufacturer has dealt appropriately with the issues raised during the previous inspection.

On June 27, 2003, Chiron sent a letter to FDA. The letter stated that Chiron wanted to meet with FDA as soon as possible to discuss its response plan and its new Quality Systems Improvements Program. FDA did not respond to the letter, as it accepted Chiron's response to the June 2003 Form 483. In a September 3, 2003 closing letter, FDA informed Chiron it would review the manufacturer's corrective actions at its next inspection. When the Committee asked Chiron about the June 27, 2003 letter, Chiron officials did not recall sending such letter or its contents. FDA explained to the Committee that manufacturers frequently send follow up letters to their response plans asking for a meeting. It is customary that if FDA accepts the manufacturer's response plan, a meeting is unnecessary. Clearly, Chiron did not persist on a meeting with FDA, as no additional letters were sent prior or after the September 3, 2003 closing date.

The Minority attempts to paint a picture of a lackadaisical Agency that had no desire to follow-up on a manufacturer's progress. FDA was following standard, across the board protocol. In fact, FDA was allowing Chiron the time it needed and is customarily provided to manufacturers to implement its corrections.

In its attack of FDA's actions, the Minority claims that FDA remained passive, while MHRA was proactive, upon learning on August 25, 2004 that some lots of Chiron's Fluvirin were contaminated. This is not accurate. There was a team of FDA officials at Chiron's Liverpool facility for an unrelated issue on August 25, 2004. FDA asked the team to visit the Fluvirin portion of the facility to gauge the situation. In addition, FDA alerted the Centers for Disease Control and Prevention and conducted weekly conference calls with Chiron to continue oversight of the situation.

When a vaccine manufacturer identifies contamination within its facility, it initiates an internal investigation to determine how the contamination occurred. Chiron initiated an internal investigation in April 2004, upon discovering contamination in some lots of Fluvirin. It is standard FDA protocol to use the internal investigative report as a tool when conducting an inspection. The report provides a roadmap for FDA to use to understand where the manufacturers stand with regard to problems at a facility.

Chiron informed FDA that it could not provide a draft report of its internal investigation until the week of October 4, 2004. FDA informed the Committee that providing the draft report by early October was within an acceptable timeframe. Upon receiving the draft report, FDA would analyze its findings and determine if an inspection of the Fluvirin facility was warranted. FDA did not receive Chiron's draft report until after the license suspension. **FDA instructed Committee staff that had the Agency received the draft report sooner, the Chiron facility would have been reinspected, whether or not MHRA suspended Chiron's manufacturing license. FDA identified severe weaknesses in Chiron's draft report and was not satisfied that Chiron properly addressed the cause behind the contamination.**

The Minority would like to paint the time between August 25 and the week of October 4, 2004 as time that FDA should have been reaching out to MHRA to determine what, if anything, they were doing with regard to Chiron. This assertion is misleading, as pursuant to the Medicines Act, MHRA is prohibited from sharing commercial information without consent from Chiron. By law, MHRA was conducting all of its actions independently from FDA. As both FDA and MHRA informed Committee staff, it is widely accepted and understood that the two Agencies do not discuss their own actions with regard to companies over which they each have jurisdiction. Since its license suspension, Chiron has permitted FDA and MHRA to communicate on all issues that concern Chiron. However, the Medicines Act is still in place in the United Kingdom.

The Minority is free to argue that they do not agree with the laws of the United Kingdom. But, to imply that FDA was passive by not urging MHRA to violate its own law, serves only to confuse those who are not well versed in FDA protocol and the United Kingdom's Medicine Act.

Of additional concern regarding the August 25 to the week of October 4, 2004 time frame, is the Minority's statements that MHRA was on top of the Chiron situation, in contrast to FDA's passiveness. This is misleading for several reasons. First, MHRA told Committee staff that it waited two weeks to respond after receiving Chiron's e-mail regarding contamination in the Fluvirin lots. Second, Chiron provided its draft internal investigation document to MHRA on September 24, 2004. The Minority may highlight that MHRA read the draft report and followed up with an investigative visit to Chiron's Fluvirin facility. The truth is that MHRA wanted to review Chiron's draft report prior to conducting its final investigative visit of the facility. Once MHRA received the draft report, a team returned to the facility on September 28-30, 2004. As Chiron claimed it couldn't provide the draft report to FDA until the week of October 4, 2004, FDA's follow up inspection of the Fluvirin facility was prolonged. **The Minority misleads Members in asserting that FDA was not conducting the same oversight as MHRA. In fact, the Chiron document both Agencies needed to proceed was provided to MHRA before FDA, hindering FDA's ability to respond with an inspection as quickly as MHRA.**

The Minority draws attention to FDA documents that indicate FDA was working with Chiron to dispel fears of a vaccine shortage. This was the responsible action for both FDA and Chiron to take. Vaccinations and the availability of preventative medicines is an emotionally charged issue. The most productive way to handle any loss of vaccine availability is to educate the public and work to decrease fear of a widespread shortage. It would be irresponsible of FDA to not lay the groundwork for how to inform the U.S. public of the possibility of a vaccine shortage.

Although the flu investigation has been conducted in a bipartisan manner, the Minority's interpretation of the information obtained by the Committee is different from the Majority's. The investigation should not be a forum for bashing FDA for following its standard accepted protocols. FDA should not be held accountable for decisions made by Chiron without its knowledge or for actions taken by MHRA that were legally

protected by laws of the United Kingdom. If the Committee keeps looking back to place blame, we will be unable to look to the future to ensure the U.S. has an adequate flu vaccine supply. If protocols need to be tweaked, we should discuss tweaking them.

Chairman Davis' main goals in the Committee investigation are to understand the lessons learned from the Chiron's license suspension and work with U.S. health officials and private industry to ensure that a similar situation does not occur in the future. After his meetings with FDA, MHRA, and Chiron, the Chairman is optimistic that Chiron will be able to produce vaccine for next year's flu season. The Chairman also recognizes the U.S. must work to expand the number of flu vaccine manufacturers that are FDA approved, so that the U.S. has more than two major vaccine companies on which to rely.

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Documents Appendix

"The Nation's Flu Shot Shortage: Where are We Today and How Prepared are We for Tomorrow?"
Government Reform Committee Hearing
November 17, 2004

1. **Form 483, June 10, 2003**: In June 2003, FDA inspected the Liverpool flu vaccine plant of the PowderJect Corporation, which was in the process of being acquired by the Chiron Corporation. FDA identified high levels of bacterial contamination (called "bioburden") in a few lots of vaccine after the ultra filtration step but before the sterile filtration process. FDA inspectors also identified sterility failure investigations that did not fully include all potential roots of contamination. FDA determined Chiron's corrective actions were incomplete. FDA inspectors identified poor sanitary practices that increased the risk that bacteria could contaminate sterile parts of the production process.

   The Form 483 is a document issued every time the FDA conducts an inspection or audit of a licensed facility. FDA inspectors use the Form 483 to list areas of concern to FDA identified during the inspection and is left with the company at the close of the inspection.

   A company has a set amount of time (usually one month) to respond to the findings and/or develop a plan to remedy any problems identified in the 483 form. If the response is deemed appropriate by FDA then the 483 process ends there and FDA expects the company to implement changes to remedy identified problems. However, if the company's response is inadequate then FDA will indicate official action and issue a warning letter. FDA found Chiron's response to the June 2003 to be adequate and was categorized as "voluntary action indicated"

2. **Establishment Inspection Report (EIR), Evans Vaccine Ltd., 2003**: In October 2003, FDA provided Chiron with a detailed report outlining its findings from the June 2003 FDA inspection of the Liverpool flu vaccine plant of the PowderJect Corporation, which was in the process of being acquired by the Chiron Corporation. FDA identified high levels of bioburden in a few lots of vaccine after the ultra filtration step but before the sterile filtration process. FDA inspectors also identified sterility failure investigations that did not fully include all potential roots of contamination. FDA determined Chiron's corrective actions were incomplete. FDA inspectors identified poor sanitary practices that increased the risk that bacteria could contaminate sterile parts of the production process.

   The EIR is a formal and more detailed description of the findings of FDA's inspection than the Form 483.

3. **Letter from Mr. A.H. Sneddon, Site Director, Evans Vaccines Ltd to K. Midthun, Center for Biologics Evaluation & Research, FDA, June 27, 2003**: The Liverpool plant's manager wrote FDA that the company would like to meet to review its response plan. The letter states, "At this meeting we would welcome the opportunity to present to the agency our Quality Systems Improvement Program."

   FDA indicated to Committee staff that it is normal procedure for any company who receives a Form 483 and develops a response plan to ask for a meeting with FDA. Once FDA reviews the company's response plan and voluntary action is indicated, no formal meeting is necessary.

4. **Letter from Philip R. Linderman, Compliance Officer, FDA to Mr. Andy Sneddon, Site Manager, Evans Vaccines Ltd, September 3, 2003**: FDA response to Sneddon's request for a meeting to review its response plan. The response states that the company's letter would be placed in its "permanent file." According to Chiron officials, no meeting ever occurred.

   FDA explained to Committee staff that it is not necessary for FDA to meet with a company that has been indicated for voluntary action. Voluntary actions do not carry the threat of legal sanction or the likelihood of a quick reinspection.

5. **Letter from Peter McBride, Regulatory Affairs Manager, Evans Vaccines to James S. Cohen, Office of Compliance and Biologics Quality, FDA, June 7, 2004**: Evans Vaccines regulatory affairs manager wrote FDA that company never received a copy of the EIR from the June 2003 inspection.

   Once an inspection is considered closed, a copy of the EIR is sent to the company. The EIR should have been issued to Evans Vaccines in September 2003. FDA admitted the delay in sending the report was a mistake resulting from miscommunication between the Center for Biologics Evaluation and Research and the Office of Regulatory Affairs.

6. **Information Alert Memo prepared by William Egan, Jerry Weir, Roland Levandowski, August 25, 2004**: CBER FDA officials prepared this memo regarding a "significant delay of release of the inactivated influenza virus vaccine produced by Chiron." The memo provides a summary of the issues, background, and Department response/actions. The memo indicates that Chiron is working with FDA and CDC to "monitor and resolve the situation."

7. **Email Communication from Elaine Cole, FDA, *Conference Call Summary-Chiron's Fluvirin*, September 9, 2004**: Email summarizes a conference call between officials from Chiron, FDA, and CDC on September 9, 2004. The purpose of the call was to "update all parties on the status of Chiron's investigation into the non-sterility of certain not-yet-marketed lots" of the Fluvirin vaccine. FDA and CDC discussed a plan to release a short statements in efforts to "dispel fears of shortages, and to state that, overall, more vaccine is expected to be available this season than last year."

   This email indicates that FDA was still expecting to receive the Chiron Fluvirin supply and did not have intimate knowledge of the widespread systemic quality control problems at the Liverpool facility.

8. **Medicines and Healthcare Products Regulatory Agency, Briefing Note: Chiron Vaccines, Speke, Liverpool, Influenza Vaccine, 1, October 5, 2004**: UK's Medicine and Healthcare products Regulatory Agency (MHRA) – the British equivalent of FDA – suspends Chiron's manufacturing license immediately for a 3 months period. MHRA sent inspectors on a "fact finding mission" to the plant on September 13 and 14, 2004. Inspectors found problems with "sterility assurance of the production process in the finished product." The decision to suspend Chiron's license "was a result of the company's failure to comply with requirements of good manufacturing practice resulting in a potentially serious risk to patients through the administration of a vaccine that may be contaminated."

   Reviewing the company's records, the British inspectors found that Chiron knew of potential contamination problems as early as April 2004. MHRA investigators also learned that sterility failures first occurred in July 2004. As a result of this information, MHRA began a fact-finding mission into Chiron's Fluvirin manufacturing facility. On September 24, 2004, Chiron provided MHRA a draft of its internal investigative report. After reviewing Chiron's draft report, MHRA conducted a full inspection of Chiron's Fluvirin facility from September 28 – 30, 2004. As part of the inspection, MHRA conducted an exit interview with Chiron to highlight MHRA's findings. The findings were then presented to the United Kingdom's Cross Agency Vaccine Inspection Action Group. The decision was made to suspend Chiron's manufacturing license for three months.

9. **Letter from Bernadette Sinclair-Jenkins on behalf of The Secretary of State for Health to Chiron Vaccines, October 5, 2004**: Letter from MHRA to Chiron to notify the company of its decision to suspend Chiron's manufacturing license in relation to influenza vaccine products. The letter cites UK's Medicines Act of 1968 and states Chiron "failed to conduct operations in accordance with the principles and guidelines of Good Manufacturing Practice." Chiron's "manufacturing and assembly of any influenza vaccine products must cease immediately." A list of findings from MHRA's September 28 through September 31, 2004 investigative visit is included with the letter.

10. **Email Communication from Norman Baylor, CBER, FDA to Jesse Goodman, James Cohen, William Egan, and Karen Midthun, October 5, 2004**: Chiron officials called Dr. Baylor to notify FDA that MHRA had suspended Chiron's "license for Fluvirin for 3 months for non-compliance with UK GMPs." Dr. Baylor also stated, "MHRA faxed us a letter this morning. I have not seen the letter nor do I know where it was faxed."

    The email confirms that FDA had no knowledge of MHRA's decision to suspend Chiron's license prior to October 5, 2004.

11. **Handwritten Notes of Internal FDA Discussions by John Eltermann, Director of Manufacturing and Product Quality, CBER, FDA, October 5, 2004**: These notes were taken during a series of teleconferences on October 5, 2004 with officials from MHRA and Chiron about the suspension of Chiron's license to manufacture. Mr. Eltermann's notes show that the June 2003 inspection of Chiron's facility was discussed internally at FDA on October 5, 2004.

    His notes indicate the "team biologics" inspectors, who conducted the June 2003 review, initially recommended that the agency indicate "official action" against the Liverpool facility. Later the recommendation was downgraded to a request for "voluntary action" by the company, which carries no legal weight.

    According to FDA officials, the decision to downgrade the enforcement action was primarily justified by the quality of the company's plan to fix the problems and by improvement in bacterial contamination noted during the 2002-2003 flu season. It is not uncommon for FDA inspectors to initially assigned "official action indicated" status to a facility after inspections. However, following several discussions and analyzing data collected during the inspection, recommendations are often revisited. The team biologics downgraded their response to "voluntary action indicated" following a complete review of information.

12. **Fax from Andy Sneddon, Liverpool Site Director, to Dr. Cohen, FDA, October 5, 2004**: Fax included a copy of "MHRA inspectorate findings together with Chiron Vaccines responses in relation to the UK facility/Fluvirin 2004 Campaign." Chiron submitted this written response to MHRA following its exit interview. However, MHRA suspended Chiron's license before responding to Chiron's responses.

13. **Email Communication from Denise Zavagano, Associate Chief Counsel for Biologics, FDA, *Questions Regarding the Suspension*, October 6, 2004**: Email from Denise Zavango to Bernadette Sinclair-Jenkins of MHRA with questions regarding MHRA's decision to suspend Chiron's license. Ms. Zavango requested a "copy of the law or regulation which provides the licensing authority in the United Kingdom with the power to order the suspension, so we can better understand how this action affects the supply of flu vaccine by Chiron."

    Questions in the email demonstrate that FDA had no knowledge of Chiron's license suspense prior to October 5, 2004. Ms. Zavango asked what, if any, course of action is available under the law or regulation that led to the suspension for Chiron to appeal the license suspension. She also inquired about the status of lots that have already been shipped from the UK and are "physically located in the USA. Who is in control of those lots and who has the authority to release them? How does the authority of the MHRA reach these lots once they have left the UK?"

14. **Draft Letter from Bernadette Sinclair-Jenkins, MHRA to Denise Zavagano, Office of General Counsel, FDA, October 8, 2004**: Draft letter is in response to Ms. Zavagano's October 6, 2004 email regarding Chiron's license suspension. "Section 28 of the Medicines Act 1968 provides powers to suspend, revoke or vary a licence under the Act. Chiron's Manufacturer's Licence was suspended with immediate effect in accordance with paragraph 11 of Schedule 2. There is no appeal mechanism for an immediate suspension."

    This letter explains to FDA the British law and regulations that led to Chiron's suspension. The letter further explains that Chiron may not appeal the license suspension. Additionally, none of the vaccines already shipped to the U.S. can be certified and released because "certification of product is a manufacturing activity."

15. **Form 483, October 9, 2004**: In October 2004, FDA inspected Chiron's Liverpool flu vaccine plant. FDA identified high levels of bioburden in final product. FDA determined Chiron had failure investigations and larger systemic issues regarding quality control.

FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
FDA/OCBQ 1401 Rockville Pike , Rockville, MD 20852. (301) 827-6101	09/02-10/03 FEI NUMBER 3002806949
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED	
TO: Andy H. Sneddon, Head of Manufacturing/Site Director Liverpool Facility	
FIRM NAME Evans Vaccines Limited	STREET ADDRESS Gaskill Road
CITY, STATE AND ZIP CODE Speke, Liverpool L24 9GR UK	TYPE OF ESTABLISHMENT INSPECTED Vaccine manufacturer

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

1) The following monovalent lots with high levels of bioburden at the [redacted] step were re-processed/re-filtered, processed into trivalent lots, and released into US market for distribution during 2001/2002 Fluvirin campaign without CBE30 and/or CBER notifications:

A) A/Panama lot #760351 with total bioburden volume of 8.48×10^9 cfu was re-filtered into lot #760591 and used in the formulation of trivalent lot #s: 760888, 760941 & 760940 and in at least final Fluvirin released lot #E10821LA.

B) A/New Caledonia lot 759931 with total bioburden volume of 3.29×10^8 cfu was re-filtered into lot #760137 and used in the formulation of trivalent lot #760843 & 760092 and in at least final Fluvirin released lot #E11041LA.

C) A/Panama lot #759864 with total bioburden volume of 4.45×10^{10} cfu was re-filtered into lot 760136 and used in the formulation of two trivalent lots 761025 & 761095 and in at least final Fluvirin release lot #E12821MA.

D.) There is no procedure that requires stability assessment of re-filtered batches, including SOP BLE024 Fluvirin Reprocessing at Monovalent and Trivalent Blend Stage. The only stability study that included re-filtered batches, R/0184/07/00 dated August 1, 2000, was not designed as refiltration protocol and assessed only previous monovalent strains, rather than those currently processed. The study also only assessed one syringe and one vial lot in one monovalent strain. The Stability Report does not include volume refiltered or pre-filtration bioburden. There is no protocol for assessment of stability of re-filtered Fluvirin when the monovalent strains change from season to season.

2) Control and failure investigations into bulk Fluvirin monovalent blends/lots at [redacted] step with high levels of bioburden is deficient, in that lots were noted with total volume of high bioburden levels of e.g., 9.86×10^8 cfu, 7.07×10^7 cfu & 1.26×10^7 cfu in year 2000/2001 and 2001/2002 campaigns and no formal investigations has been opened to find the root cause of the high levels of bioburden in these lots.

3) There is no documentation that the decisions to continue with the manufacturing of the Fluvirin monovalent lots with high levels of bioburden levels were based on the pathogenicity of the organisms that were isolated from the sampled lots. e.g., gram negative; *Serratia marcesens*, *Enterobacter cloacae*, and *Pseudomonas putida*.

4) Sterility failure investigations do not fully include all potential roots of contamination and corrective actions are incomplete. For example,

A.) The NCR investigations of Monovalent Blend Pool Batch #762492 refiltered into Batch #762835 dated July 2002 and batch # 761660 dated May 2002 implicated aseptic connections as potential root causes but failed

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		Omotunde O Coumanni, CSO Robert W. Jennings, CSO Robin Levis, Ph.D. Regulatory Coordinator Jonathon McInnis, Biologist	9/10/03

FOOD AND DRUG ADMINISTRATION

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FDA/OCBQ 1401 Rockville Pike, Rockville, MD 20852 (301) 827-6191	09/02-10/03
	FEI NUMBER 3002806949

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Andy H. Sneddon, Head of Manufacturing/Site Director Liverpool Facility

FIRM NAME	STREET ADDRESS
Evans Vaccines Limited	Gaskill Road
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Speke, Liverpool L24 9GR UK	Vaccine manufacturer

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to result in procedural requirements for environmental monitoring during all aseptic connections and evaluation of possible reductions in the number of aseptic connections.

B.) Settling plates were placed on the formulation tank at least 15 minutes after aseptic connections to the tank during the formulation of New Caledonia lot # 764964 observed on June 4, 2003. Viable and non-viable monitoring was initiated at least one hour after all connections were made including those to the [redacted] unit which are made in Class [redacted] conditions [redacted]

C.) Klebsiella oxytoca was isolated in the Centrifugation [redacted] batch 762460 and the [redacted] Zonal Concentrate batch #762451 that went into batch #762492. K. oxytoca was also isolated in the [redacted] filtration sample as well as the sterile-filtered sample. There was no investigation of water monitoring results or environmental monitoring results prior to this batch.

D.) From February 28 2002 to July 5, 2002, 14 [redacted] Monovalent Blend Pools failed bioburden testing with a Klebsiella isolate. Closure of the sterility failure investigation of lot# 762835 (refiltered from lot# 762492) on July 9, 2002 did not include reference to nor investigation of the additional failed batches with the same isolate.

E.) There was incomplete review and approval justification for retests in sterility OOS test results reviewed for 2001 and 2002.

5) The following deficiencies were noted in product contact equipment compatibility:

A) There is no filter compatibility and extractable validation studies on filtered Fluvirin monovalent and/or trivalent bulks. In addition, filter compatibility was not considered in the product stability failure investigations. As such, filter compatibility studies has not been eliminated as the reason for loss of potency after the trivalent filtration step that resulted in failures of four out of five Fluvirin lots placed on stability for year 2001/2002 campaign.

B) The [redacted] tubing used throughout the Fluvirin manufacture process to transfer centrifuged, formulated and finished product for filling was out of specification of [redacted] mg for USP Non-Volatile Residue with result of 1327 mg per [redacted] test result. No investigation, corrective and preventive action has been conducted and no justification/rationale is provided for lack of investigation.

6) The investigation into the reported Fluvirin potency stability test failures in 2001/2002 and 2002/2003 was incomplete. For example,

A.) The conclusion implicating CBER reagents in the test failures was not fully justified. The study did not address that failures primarily occurred only after 6 months on stability. Root cause(s) have not yet been identified, including potential contributing factors specific to the antigen and antiserum and the investigation is ongoing.

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	O. Cleveland Robert W. Jennings	Omotunde O Cleveland, CSO Robert W. Jennings, CSO Robin Levis, Ph.D. Regulatory Coordinator Jonathon Mcinnis, Biologist	9/10/03

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED	FEI NUMBER 3002806948
TO: Andy H. Sneddon, Head of Manufacturing/Site Director Liverpool Facility	

FIRM NAME	STREET ADDRESS
Evans Vaccines Limited	Gaskill Road
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Speke, Liverpool L24 9GR UK	Vaccine manufacturer

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B.) The manufacturing investigation did not include a failed 2000/2001 batch and 2001/2002 batches reviewed were not fully identified in the report (Appendix 14). The root cause investigation was not included in the report.

C.) There was no review and approval of the Summary Report investigation into Fluvirin Stability Results by management involved in the investigation. The Summary Report is not dated.

D.) There was no review and approval of the draft Clinical Expert Report dated September 4, 2002 justifying the firm's decision not to execute product recall. The author of the report is not identified and did not sign the report.

7) The Biological Product Deviation (BPDR) reported June 28, 2002 for reported Fluvirin potency and pH stability test failures was incomplete and failed to provide FDA significant information for timely evaluation. Additionally, there is no justification for management's failure to identify the significance of failing and missing test results during review and approval of the results and the ongoing stability program as required by Stability Policy Document SOP041. For example,

A.) The firm simply reported that OOS potency and pH test results had occurred and no failing test results, including failing New Caledonia potency test results and stability test time points (specification minimum [redacted] mcg HA per SRID), were submitted.

B.) Although the firm reported that a failure had occurred for lot# E00031HA, they did not report that the initial failure of the 2001/2002 season (26.8 mcg) occurred at the scheduled 6-mo test point reported February 10 2002, over 5 months prior to BPDR submission. The lot also failed at the 9-mo test point (24.9 mcg) in May 2002 and the 12-mo test point (13.1 mcg). The firm did not have a rounding procedure and reportedly did not consider 26.8 mcg a failure-no report to FDA was made for the 6-mo result.

C.) No information was submitted to FDA on lot #s E12201MA (24.1 mcg) and E11371LA (21.9 mcg) which failed when first tested on stability at the 7-mo test point on May 25, 2002. Required tests at the 1, 2, 3 and 6-month time points were not executed-this was not reported to FDA. No NCR was initiated for missed time points and failure to submit BPDRs and no justifications have been written. Limited data on these lots were submitted without full explanation in the related September 4, 2002 BPDR. Shelf-life Stability Summary Reports for the two lots, reviewed and approved by QA, QC and RA in January 2003, failed to report and evaluate missed time points in the studies.

8) No BPDR was submitted for the Fluvirin pH OOS (7.9) at the 3-month test point on December 18, 2002 for lot # E34852KA 2002/2003 season. A follow-up report to the September 4, 2002 BPDR was not submitted in which the firm reported that additional OOS pH results were likely to occur in other batches.

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FOOD AND DRUG ADMINISTRATION

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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Andy H. Sneddon, Head of Manufacturing/Site Director Liverpool Facility

FIRM NAME	STREET ADDRESS
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CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Speke, Liverpool L24 9GR UK	Vaccine manufacturer

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9) Corrective action has not been implemented for the previous FDA 483 observation regarding the failed [redacted] System cleaning validation study CVR/0016/00 dated August 16, 2000. For example,

A.) The firm's response to the previous FDA 483 stated the evaluation of the study concluded there was no impact on Fluvirin. From March 2001 through 2002 at least 50 [redacted] Monovalent Blend Pool lots failed bioburden testing.

B.) Validation protocol for the executed study CVP/0011/03 dated April 7, 2003, changing the sanitizing agent to [redacted] did not include bioburden reduction by assessing microbial load prior to use or storage between uses.

C.) Design and operation of the [redacted] filtration unit located in the Formulation area allows operator error to potentially reverse the flow of product under filtration. The [redacted] has a piece of masking tape over the flow direction dial on which is written "Do Not Use". Use of the flow director would reverse the flow of product. The dial is located next to another dial that requires regular use for pressure regulation.

10) It was noted during the observation of formulation of A/New Caledonia Monovalent Blend Pool batch # 764984 on June 4, 2003 that sub-batch [redacted] samples were not taken as required (per SOP ZY033A Release of [redacted] Concentrate to the Formulation Department including the [redacted] day ruling) [redacted] days after the [redacted] centrifugation run on May 22, 2003. There are no procedures to assure samples are taken and there is no information this deviation had ever been previously identified. The NCR investigation to determine additional batches affected by similar deviations was reportedly ongoing.

11) The following was noted during vial filling on June 6, 2003 (under Protocol P/0097/04/03):

A.) There was no documentation in the batch record of missed stoppers or seals and there is no procedural requirement to do so.

B.) A panel, about 8 by 10 inches, was open in the cabinet under the filling machine and there was no information on the length of time this condition had existed or that correction had been scheduled. The open panel area could allow the accumulation of potential contaminates under the filling machine that would be difficult to clean/sanitize.

C.) An operator was noted to be pushing curtains into the area near open empty vials while retrieving tipping vials on 2 occasions disrupting vertical laminar flow.

D.) 2 plastic yellow beakers used for holding forceps were scratched and yellowed.

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	O. Osunsanmi Robert W. Jennings	Omotunde O Osunsanmi, CSO Robert W. Jennings, CSO Robin Levis, Ph.D. Regulatory Coordinator Jonathan Mcinnis, Biologist	6/10/03

FORM FDA 483 (4/03) PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATIONS PAGE 4 of 8

FOOD AND DRUG ADMINISTRATION

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AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED	FEI NUMBER 3002806949
TO: Andy H. Sneddon, Head of Manufacturing/Site Director Liverpool Facility	

FIRM NAME	STREET ADDRESS
Evans Vaccines Limited	Gaskill Road
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Speke, Liverpool L24 9GR UK	Vaccine manufacturer

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12) Regarding sanitizer efficacy validation study protocols,

A.) Study R/0083/05/01 Evaluation of Disinfectant Products using Qualitative European Surface Tests for both Bacteria and Fungi dated July 13, 2001 failed to include the full range of cleaning agents (i.e. [redacted] and manufacturing surfaces (i.e. laminate on doors, Perspex on filling unit curtains). Additional studies, i.e. PQP/0028/01, did not assess cleaning efficacy on manufacturing surfaces.

B.) Acceptance criteria were not met for Study R/0083/05/01 against bacteria including spore-formers and mold and no additional protocols have been written/executed.

13) No protocol deviation was initiated for the failure to execute the portion of Protocol PVR/0005/01 Determination of effects of Holding Times on the potency of Fluvirin Monoblend Pools, requiring that a routine batch be placed on stability. The summary report, reviewed and approved by QA on January 30, 2003, reported that the routine batch was not placed on stability while also stating that no differences between the test batch and routine batch were observed. Another protocol was not executed.

14) Regarding Batch records including review, approval and batch release,

A.) Procedures do not assure full review of deviations prior to release. Worksheets to assure QA batch record review and product release are not included in written procedures, i.e. QA Bulk Trivalent Checklist (not in SOP QASP093 QA Procedure for Review of Finished Product) and Fluvirin Trivalent Vaccine Product Release Checklist (not in SOP PRG020 Release of Finished Products from Quarantine), i.e. Trivalent batch # 762834, filling batch #762925 and Packing batch #E31192HA released September 4, 2002.

B.) An incorrect NCR was referenced in the batch record for the sterility test for batch # 762834.

C.) Labels for working seed cell culture vials are not maintained in the Manufacturing Instruction batch records, i.e. B/Hong Kong/330/01 lot# [redacted] Evans [redacted] passage dated October 25, 2002.

D.) There was no documentation in the filling batch record of a leak in filling tubing causing the filling process to abort for lot# 762838 on June 6, 2002. Although an NCR was initiated, there is no evidence in the batch record the leak occurred.

15) There is no requirement for investigation of consecutive, repeated alert level sample results for water monitoring as allowed by SOP M154 Water Monitoring Excursion Reports.

16) The following deficiencies were noted in the Fluvirin media fill simulations:

A) Media fill simulations are not representative of actual aseptic filling process in that interventions that occurred during aseptic filling processes are not evaluated and considered for incorporation into media fill simulations.

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	O. Oluwasanmi Robert W. Jennings	Omotunde O Oluwasanmi, CSO Robert W. Jennings, CSO Robin Levis, Ph.D. Regulatory Coordinator JaneSue McInnis, Biologist	9/10/03

FORM FDA 483 (4/83) PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATIONS PAGE 5 of 6

FOOD AND DRUG ADMINISTRATION

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B) Worst case conditions to be conducted during media fill simulations are not defined in SOP # SCP029 dated 9/9/02: General Procedure for Routine Monitoring of Aseptic Manufacturing Processes by Process Simulation Utilizing Sterile Media Fills and/or Performance Qualification Protocol # PQP/0057/01.

17) There was no documentation that adverse events (AE) reported for vaccine season 2002/2003 with the same lot numbers reported by different Health personnel/facilities on Fluvirin batches were reviewed, evaluated and/or investigated to determine if the adverse event may be related to the manufacturing process, for example:

A) Ten adverse events reported for batch #E35732HA on injection sites inflammation by eight different healthcare facilities.

B) Five adverse events reported on batch #E33922HA on injection sites inflammation by five different healthcare facilities.

C) Forty-one adverse events reported on batch #E33402HA on injection site reactions reported by two healthcare facilities.

18) Temperature mapping study has not been conducted for the [redacted] degrees centigrade) freezer, Serial [redacted] used in the storage of frozen master and working seeds used in the manufacture of Fluvirin. (Protocol # IOQP/0040/03 dated 5/19/03 for the qualification of the freezer is currently in place).

19) The following deficiencies were noted in the 100% Fluvirin finished vials visual inspections:

A) The 100% visual inspection and re-inspection of finished Fluvirin vials defects are not based on acceptable statistical sampling plans and/or review of historical data but based on [redacted] reject/accept rate that was used to set the initial limits.

B) The 100% visual re-inspections of finished Fluvirin vials are not based on a tighter sampling plan but are conducted at the same accept/reject rate of [redacted] as the initial 100% visual inspections.

C) Critical and non-critical finished vials inspection defects are not defined in SOP #IN017.V1 dated 8/13/01; General Procedure for Performing Re-examination in Manual and Semi Automatic Inspection. In addition, all vial defects are based on the same reject/accept rate of [redacted] for, e.g., appearance, particles, broken glass, empty vials, and seals.

D) There is no Quality Assurance control/verification and/or over site of the 100% finished vials inspection for defects that are performed by manufacturing.

20) SOP #IN018 dated 5/25/03 for the training of Fluvirin 100% finish vials inspection personnel is incomplete, in that it failed to include the length of training of personnel for finished Fluvirin vials defect inspections and the level of supervision of the trained personnel after training.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	[signature]	Omotunde O Osunsanmi, CSO Robert W. Jennings, CSO Robin Levis, Ph.D., Regulatory Coordinator Jonathan McInnis, Biologist	8/10/03

The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under unsanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."

ESTABLISHMENT INSPECTION REPORT 1

EVANS VACCINE, Ltd.
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DATES OF EI: 6/02-10/03.

SUMMARY OF FINDINGS:

This inspection of a foreign manufacturer of licensed Flu Vaccine Product (Fluvirin) was conducted pursuant to Core Team Biologics FY'03 Workplan. This inspection was conducted in accordance with CP 7345.002 Inspection of Licensed Vaccine Product. In addition, assignment from the Office of Compliance and Biologics Quality, Division of Inspections and Surveillance dated 5/16/03 was also covered during this inspection.

The previous PAI inspection dated 5/11/01 was for a new ---------- Syringe filling line and deficiencies were noted in the firm's manufacturing process, such as: lack of documented failure investigations, failure to close non-conformances within time frames, deficient equipment cleaning and autoclave validations, and lack of documentation of the inspection of media filled units. FDA-483 was issued and the firm promised corrective actions.

The cGMP inspection of 3/09/01 disclosed deficiencies in Fluvirin process validation, the cleaning validation of the ---------- System and lack of validation of the ---------- Vial Filler speed and vial/stopper washing process. In addition, failure of non-conformance reports to include adequate information, e.g., bioburden levels and correct dates of microbiology laboratory notifications were noted. Deficiencies were also noted in sterility test failure investigations, inaccuracies in Master Production Records, WFI sample collection for routine monitoring, and failure of the Quality Control Unit to conduct monitoring of various production operations. FDA-483 was issued and the firm's officials promised corrective actions.

This inspection disclosed the firm has corrected most of the observations that were cited during the PAI and cGMP of 5/11/01 & 3/09/01. However, this inspection noted inadequate corrective actions to Observations #1C, 7, 11, 20 & 28 for the cGMP inspection dated 3/9/01. Deficiencies were also noted during the review of FDA-483 issued during the PAI inspection 5/11/01. For discussion on deficiencies noted during the review of corrective actions to FDA-483 issued during the cGMP and PAI inspections, please see discussions in this EIR under corrective actions to previous observations.

The current inspection revealed the following deficiencies in the firm's manufacturing operations for Biologic products:
At least there monovalent lots with high levels of bioburden at the ---------- step were re-processed/re-filtered and processed into trivalent lots, and released into US market for distribution during 2001/2002 Fluvirin campaign without CBE30 and/or CBER notifications. In addition, there is no procedure that requires stability assessment of re-filtered batches, including SOP BLE024 Fluvirin Reprocessing at Monovalent and Trivalent Blend Stage. Control and failure investigations into bulk Fluvirin monovalent

blends/lots at---------- step with high levels of bioburden is deficient, in that lots were noted with total volume of high bioburden levels of e.g., $9.66x10^6$ cfu, $7.07x10^7$ cfu & 1.26×10^7 cfu during year 2000/2001 and 2001/2002 Fluvirin campaigns and no formal investigations has been opened to find the root cause of the high levels of bioburden in these lots. Also, there is no documentation that the decisions to continue with the manufacturing of the Fluvirin monovalent lots with high levels of bioburden were based on the pathogenicity of the organisms that were isolated from the sampled lots, e.g., gram negative organisms such as: *Serratia marcesens, Enterobacter cloacea*, and *Pseudomonas putida.*

The inspection noted the lack of filter compatibility and extractable validation studies on filtered Fluvirin monovalent and/or trivalent bulks and the---------- --------- Tubing used throughout the Fluvirin manufacturing process to transfer centrifuged, formulated and finished products for filling was out of specification of --- mg for USP Non-Volatile Residue with result of 1327 mg per ---------- test result. Also, the inspection noted incomplete investigations into the reported Fluvirin potency stability test failures for year 2001/2002 and 2002/2003. Additionally, the Biological Product Deviation (BPDR) reported on June 28, 2002 and the reported Fluvirin potency and pH stability test failures in the BPDR were incomplete and failed to provide FDA with significant information for timely evaluation.

Furthermore, the inspection noted that corrective action has not been implemented for the previous FDA 483 observation regarding the failed---------- System cleaning validation study CVR/0016/00 dated August 16, 2000. It was also noted during the observation of the formulation of A/New Caledonia Monovalent Blend Pool batch # 764984 on June 4, 2003 that ---- -batch endotoxin samples were not taken as required (per SOP ZY033A Release of ------- ---------- Concentrate to the Formulation Department including the - -day ruling) ----- days after the ---------- --- centrifugation run on May 22, 2003.

In addition, during the June 6th 2003 walk through of the firm's facility it was noted that there was no documentation in the batch record regarding missed stoppers or seals and there is no procedural requirement to do so. Also, a panel about 8 by 10 inches, was open in the cabinet under the filling machine and there was no information on the length of time that this condition had existed or that repairs had been scheduled. Furthermore, an operator was noted to be pushing curtains into the area near open empty vials while retrieving tipping vials on 2 occasions disrupting vertical laminar flow and 2 plastic yellow beakers used for holding forceps were observed scratched and yellowed.

Furthermore, deficiencies were noted in the sanitizer efficacy validation study protocols, batch records review, approval and batch release documentation. In addition, failure to have requirement for investigation of consecutive, repeated alert level sample results for water monitoring as allowed by SOP M154 Water Monitoring Excursion Reports was

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noted. Also, deficient Fluvirin media fill simulations, adverse events (AE) investigation to determine if the adverse event may be related to the manufacturing process and failure to conduct temperature mapping study for the ---------- degrees centigrade) freezer were documented during this inspection.

At the close of the inspection, FDA-483, Inspectional Observations was presented to, Mr. Andy H. Sneddon, Site Director for Liverpool who identified himself as the most responsible official located at the firm even though Mr. Staph Bakali, Director of Operations for PowderJect Pharmaceuticals was present at the firm during the issuance and discussion of the FDA-483. Mr. Sneddon acknowledged the receipt of the observations and promised corrective actions. For a list of the firm's personnel present during the FDA-483 issuance, see **Exhibit #OOOA.**

HISTORY OF BUSINESS:

The firm continues to be a manufacturer of one licensed flu vaccine referred to as Fluvirin and other bio-pharmaceutical products that are not imported into the United States. It should be noted that Evans Vaccine is a Wholly Owned Subsidiary of PowderJect Pharmaceuticals with headquarters located at PowderJect Pharmaceuticals plc, Robert Robinson Avenue, The Oxford Science Park, Oxford OX4 4GA, United Kingdom. The firm's history of business including manufactured products remains the same as stated in the previous EIR of 3/01. According to Mr. John O'Brien, Head of Operations, the firm currently has ----- employees. He also stated that the firm's business hours are 8:00am to 4:45pm and manufacturing hours are usually 24 hours/day 7 days/week.

Per Mr. O'Brien, the firm made several significant changes in its officials since the last inspection of 3/01. Mr. O'Brien stated Mr. Jim Williams was added to CBER Official Correspondent for United States, and that Mr. Andy Sneddon currently holds a newly created position of Head of Manufacturing and Site Director replacing Mr. Joseph Caldwell who was previously the Managing Director of Evans Vaccine. Also that Mr. Simon Bryson Head of Quality replaced Peter Earps, who was promoted to the position of VP of Quality.

For documentation of the firm's interstate commerce provided by Dr. Tony Pawson, Quality Assurance Manager, see **Exhibit #OOOB**.

For a list of consultants provided by Mr. Tony Pawson, Quality Assurance Manager, see **Exhibit #OOOC.**

For a list of the firm's personnel that assisted the Investigators during the inspection and Firm's Annual Report, see **Exhibit #OOOD & E.**

ESTABLISHMENT INSPECTION REPORT 4

EVANS VACCINE, Ltd.
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DATES OF EI: 6/02-10/03.

INDIVIDUAL RESPONSIBILITIES/PERSONS INTERVIEWED:

On June 2nd 2003, credentials of Omotunde O. Osunsanmi, CSO (Lead), Robert W. Jennings, CSO, and Jonathan McInnis, Biologist were presented to Mr. Andy Sneddon, Head of Manufacturing/Site Manager who identified himself as the most responsible official for Evans Vaccine manufacturing. Present during the credentials presentation were: Mr. Jim C. Williams, VP of US Regulatory Affairs; Mr. Simon P. Bryson, Head of Quality; John O'Brien, Head of Operations for Liverpool. Also, on June 3rd 2003 credentials of Ms. Robin Levis, Ph.D., Regulatory Coordinator were presented to Mr. Sneddon in the presence of the above named firm's officials. The investigation team was later introduced to Mr. Staph Bakali, Chief Operating Officer of PowderJect and member of the Board who was on one of his regularly scheduled visit to the firm.

According to Mr. Staph Bakali, Chief Operating Officer, he has been with the firm since year 2001. Per Mr. Bakali, he is responsible for the firm's overall operations, which includes quality assurance/assuring regulatory product compliance, environmental health, sales and marketing. According to Mr. Bakali, he visits this Evan's facility twice per month for two to three days. Mr. Bakali stated he reports directly to Mr. Paul R. Drayson, CEO and also a member of the Board. Mr. Bakali was not present during the inspection. **If necessary all Correspondences regarding this inspection should be sent to Mr. Bakali at his official business address of PowderJect Pharmaceuticals plc, Robert Robinson Avenue, The Oxford Science Park, Oxford OX4 4GA, United Kingdom and/or Mr. Andy Sneddon at the above firm's EIR official business address.**

Andy Sneddon, Head of Manufacturing/Site Manager: According to Mr. Sneddon, he has been with the firm since December 2001. Per Mr. Sneddon, he has Degrees in Pharmacy and Pharmacology. Mr. Sneddon stated he is responsible for this facility manufacturing, engineering operations, and business improvement. Also that he reports directly to Mr. Staph Bakali, COO. According to Mr. Sneddon, he is part of product recall committee and responsible for informing his superiors on product recall. Per Mr. Sneddon, he could spend up to ---------- without prior approval for corrections to FDA-483 observations and to make improvements in the manufacturing facility.

Simon Bryson, Head of Quality: per Mr. Bryson, he has been with the firm since June of 2003 and has a degree in Biochemistry with Post-graduate Degree in Pharmaceutical Sciences. According to Mr. Bryson, he is responsible for all product quality activities at this facility, validation, quality systems/compliance, quality control, quality assurance operations and third party vendor quality assurance.

For the firm's current organizational chart as well as Quality Assurance/Regulatory Affairs organization charts, see **Exhibit #OOOF.**

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For maps of Evans Vaccine manufacturing sites provided by Mr. Tony Pawson, see **Exhibit #OOOG.**

CBER Special Assignment Requests:

(RL)

1) Review of Annual Report: Review of annual report for year 2001-2002 revealed no objectionable conditions.

(RL/RWJ)

2) Review of Biological Deviations:

Please see discussion under **Observation #s 7 & 8** of this EIR

(OOO)

3) Review of Complaints/Adverse Experience Files: No objectionable conditions were noted during the review of complaints for all Fluvirin vaccine products manufactured and distributed. For deficiencies noted during the review of the adverse event files please see discussion under **Observation #17** of this EIR.

(RL)

4) Review of Bovine Spongiform (BSE):
The firm does not use any bovine containing materials in their manufacturing process.

5) Product Shipping Validation:

(RL)
Please see discussion under (RL) titled "Discussion Items" of this report.

Corrections to Previous FDA-483 cGMP Inspection dated 3/09/01:

(OOO)

The inspection revealed the firm has adequately corrected Observation #1A, 1B, 2, 3, 4, 5, 6, 8, 9, 10, 12, 13, 14, 16, 17, 18, 19, 21, 22, 23, 24, 25, 26, 27, 29, 30 & 31.

ESTABLISHMENT INSPECTION REPORT 6

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DATES OF EI: 6/02-10/03.

The following observations have not been adequately corrected: 1C, 7, 11, 20 & 28.

Observation #1C: *The cleaning validation study for the ---------- -------- System (CVR/0016/00) failed to meet the acceptance criteria in at least one of the three runs for conductivity, formaldehyde or bioburden.* Please see discussion under **Observation #9** of this report.

Observation #7: *Inaccuracies were noted in the Master Production Records (Manufacturing Instructions MI) for Fluvirin.....*

Although the inspection noted that corrections were made to the observation, but the deficiencies noted during the previous EI continued as noted and discussed under **Observation #14** of this EIR.

Observation #11: *The-- ------ -- --- Vial Filler did not have a validated filling speed....*

Deficiencies were noted in the firm documentation of validation of the vial filling speed. It was noted that only the speed of the vial filling machine was validated, time, and pressure of the vial over seal were not part of the validation. In addition, there was no documentation that the operation parameters of the vial sealing machine per the SOP were reviewed and considered during the validation. Mr. O'Brien agreed with the observation and promised corrective action.

Observation #20: *During July through December 2000, 15 of 250 WFI samples collected revealed the presence of microorganisms. These samples were collected between 7:00-8:30AM daily when ambient loop - C began to cool down to ---C.....There is no provision for periodic steam or chemical sanitization of loop - C distribution.*

The inspection noted that the above observation was corrected. However, the review of SOP #GEP408 Version #1 dated 11/7/02 disclosed that the WFI loops are sanitized once every ----------. I informed Dr. Pawson that the whole WFI system should be sanitized at least once/year. Dr. Pawson agreed to consider my suggestion.

Observation #28: *There is no testing performed to determine the compatibility of the vaccine formulations with the manufacturing equipment.*

Please see additional discussion under **Observation #5** of this EIR on the inadequacy of the corrective action to the observation.

ESTABLISHMENT INSPECTION REPORT 7

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DATES OF EI: 6/02-10/03.

Corrections to Previous FDA-483 Pre-Approval Inspection dated 5/11/01:

(RWJ)
Corrective actions to the FDA 483 issued for the PAI of May 2001 were covered and found to be generally adequate. No reporting of those determined to be fully adequate will be made. The corrective actions to an observation noted to be not fully adequate which required focused coverage during the current inspection included:

1. The corrective action included simply a brief post-event investigation report stating that no root cause was found for the three environmental excursions that resulted in batch rejection. There was no detail provided as to how the firm attempted to determine contributory factors to the excursions. Although the firm combined several types of deviations into the NCR system, the NCR SOP was noted to lack procedures for root cause investigation, including instructions for investigations which do not result in a clearly assignable route cause. Investigation procedures were reported on the current FDA 483.

PRODUCT COVERED DURING THIS INSPECTION:

(OOO)
Influenza Virus Vaccine (Fluvirin): The license holder for Fluvirin is Evans Vaccine, a sterile parenteral for intramuscular use. Fluvirin is a purified split virus preparation from the extra-embryonic fluids of embryonated chicken eggs which contain the virus that is harvested and clarified by centrifugation and filtration prior to inactivation with betapropiolactone. The inactivation is concentrated and purified by zonal centrifugation. Dr. Pawson provided me with lists of monovalent, trivalent and finished lots of Fluvirin manufactured since the last inspection, (**Exhibit #OOO1J & 1K**). For Fluvirin manufacturing flow chart, see **Exhibit #OOOH.** For Fluvirin product insert, see **Exhibit #OOOJ.** For a list of Fluvirin distributors in the United States provided by Mr. O'Brien, see **Exhibit #OOOK.**

INSPECTIONAL COVERAGE:

This inspection was conducted in accordance with CP 7345.002 Inspection of Licensed Vaccine Product.

The following systems/areas were covered during the cGMP inspection:

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(OOO)
Adverse events/complaints/recalls, water system maintenance/trends, microbiology laboratory OOS, In-process/finished product failure investigations, validations of critical manufacturing parameters, e.g., bulks/buffers hold times, media fills/aseptic filling operation, cleaning validations and environmental monitoring/trending/excursions specific to manufacturing locations of Fluvirin product.

No significant observations were noted in the review of the trend data for water system maintenance and environmental monitoring.

(RWJ)
Coverage included, but was not limited to the following areas in addition to routine Compliance Program coverage: environmental/water monitoring & excursions, cleaning validation/cleaning procedures/sanitizer efficacy studies, smoke studies (observed for syringe filling line), batch records and quality batch review/release, sterility failures, re-filtration, non-conformance investigations, centrifugation, ultra-filtration, aseptic processing, working seed passages, re-fortification, quality management controls, stability program, Biological Product Deviation Reporting, process validation, and sterilization of vials/stoppers. In addition, set-up and formulation of monovalent/trivalent lots and set-up and vial filling operations were observed during this inspection.

(RL)
Inspection coverage included the following areas of the firm and product manufacture: Review of BLAs, process flow charts, Product Quality Specifications for bulks and final product, process validation studies, QA/QC GLP laboratories, BLA annual reports, annual product reviews, stability program and data for product, biologic product deviation reports, out of specification log and reports, process deviation log/ nonconformance reporting, rejected lots and batches released, review of BSE, and product shipping procedure and validations.

Unless specifically stated as an observation or a discussion item the review of the above items are satisfactory.

OBJECTIONABLE CONDITIONS/DISCUSSIONS WITH MANAGEMENT:

Prior to the discussion of each FDA-483 item, the firm's management was advised that the findings were observations made during the inspection. It was further stated that the conditions observed might be determined by the FDA after review of all the facts to be violations.

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1) The following monovalent lots with high levels of bioburden at the ---------- step were re-processed/re-filtered, processed into trivalent lots, and released into US market for distribution during 2001/2002 Fluvirin campaign without CBE30 and/or CBER notifications:

A) A/Panama lot #760351 with total bioburden volume of $6.48x10^9$ cfu was re-filtered into lot #760591 and used in the formulation of trivalent lot #s: 760688, 760641 & 760640 and in at least final Fluvirin released lot #E10821LA.

B) A/New Caledonia lot 759931 with total bioburden volume of $3.29x10^9$ cfu was re-filtered into lot #760137 and used in the formulation of trivalent lot #760843 & 760092 and in at least final Fluvirin released lot #E11941LA.

C) A/Panama lot #759864 with total bioburden volume of $4.45 x10^{10}$ cfu was re-filtered into lot 760136 and used in the formulation of two trivalent lots 761025 & 761095 and in at least final Fluvirin release lot #E12821MA.

(OOO)
The review of failure investigations into flu vaccine batches for the year 2001/2002 flu campaign disclosed the above noted observations. The inspection noted that monovalent batches of flu vaccine with initially high bioburden levels after the ---------- step were re-filtered due to high bioburden levels before they were combined with the remaining two monovalent batches to make the final trivalent flu vaccine lots. The high levels of bioburden resulting in re-filtration/rework of the monovalent lots were brought to the attention of Mr. Tony Pawson, Quality Assurance Manager and he informed me that since the firm was informed during the last cGMP inspection that re-filtered flu batches are considered reworked and not to be distributed without CBER knowledge that none of the re-filtered monovalent lots were distributed in the United States. It was noted that the cGMP Inspection Report dated March 9th 2001 page #21, paragraph titled: Regarding Fluvirin reprocessing SOP states:

"The reprocessing SOP has been changes to reflect current procedures, and acceptance criteria. Medeva has decided not to include the re-filtration re-process step for Fluvirin distribution in the United States. If this step is required for the US lot they will submit the necessary information for approval prior to distribution. I asked that the SOP reflect that reprocessing step for re-filtration states that this is not yet approved for US Fluvirin lots".

Although the discussion took place during the inspection dated March 9th 2001, the above reference SOP #BLE024 dated December 20th 2002 titled: Fluvirin Reprocessing at Monovalent and Trivalent Blend Stage was not revised until 12/20/02, **(Exhibit #OOO1L).** Also, re-filtration of Fluvirin lots continued after it was discussed with the firm

during the inspection. Per the review of the three re-filtered lots in the above Observation #s 1A, 1B & 1C non-conformance initiation dates for the lots high bioburden levels/re-filtration were: August 30th 2001, July 27th 2001 and July 19th 2001 respectively.

My review of the monovalent lots with the high bioburden levels and the final/released trivalent flu lots disclosed that some of these monovalent lots were indeed used in trivalent lots that were released into the US market as stated in the above observations. My concerns regarding the observations of high bioburden/re-filtered/reworked monovalent lots was discussed again with Dr. Pawson and I was informed that the firm has approval from CBER to re-filter Fluvirin monovalent lots and that the firm's regulatory affairs department was searching for the approval correspondence and will present me with the approval letter. I was also asked to give the firm's management time to review the rework/re-filtered approval documents in order to present me with chronological correspondences with CBER regarding re-work/re-filtration of monovalent flu batches. As such, time was set for the presentation of the documentation for later on during this inspection.

The presentation of the presumed approval letter for re-filtration was presented by Simon Bryson, Head of Quality and Dr. Pawson in the presence of Mr. John O'Brien, Head of Operations. Per Mr. Bryson, the firm does not have documentation of an approval letter from CBER to re-filter monovalent flu batches. He further stated that after the inspection of 3/01 when the discussion on re-filtered batches were raised the firm was informed by the Investigations that CBER notification regarding re-filtered monovalent batches was needed before the final vials of the trivalent lots could be distributed. Per Mr. Bryson, the firm responded to CBER with reworked/reprocessed SOP and the firm's assumption was that it was okay to re-process monovalent lots with high bioburden levels. He stated that after further consideration in year 2002 the firm decided not to re-filter any monovalent flu lots designated for US distribution. He also stated that the noted re-filtered lots that went into trivalent lots and final vials for US distribution as noted by me during this inspection were released into US market by mistake. Mr. Bryson promised immediate corrective actions.

The inspection noted that at least 6 re-filtered monovalent lots that were further processed into trivalent lots were filled into final vials with some of these lots packaged for US market distribution. For example:

The inspection noted that monovalent A/Panama batch #760351 with total bioburden volume of $6.48x10^9$ cfu was re-filtered into lot #760591 and was used in the formulation of trivalent lot #s: 760688, 760641 & 760640 and in at least final Fluvirin released lot #E10821LA. For initial monovalent batch record #760351 and evidence that the lot was re-filtered into lot #760591 and documentation of bioburden levels test results for before and after re-filtration, see **Exhibit #OOO1A1, page #1 & page #8, 12-15**.For, trivalent

lots 760688, 760641 & 760640 that were made from re-filtered lot # 760591, see **Exhibit #OOO1A2, 1A3, 1A4, 1F & 1G**.

Furthermore, monovalent A/New Caledonia batch 759931 with total bioburden volume of $3.29x10^9$ cfu was re-filtered into lot #760137 and used in the formulation of trivalent lot #760843 & 760092 and in at least final Fluvirin released lot #E11941LA. For initial monovalent batch record # 759931 and documentation of bioburden levels test results before and after the re-filtration process, see **Exhibit #OOO1B1 page # 8-10,** For trivalent batch records for 760843 & 762920, see **Exhibit #OOO1B2, 1B3, 1F & 1G).** Please note the indications on **page #1 of Exhibit #OOO1B1** that batch #759931 was re-filtered into lots 760137 for further processing.

Also, monovalent A/Panama batch #759864 with total bioburden volume of $4.45\ x10^{10}$ cfu was re-filtered into lot 760136 and used in the formulation of two trivalent lots 761025 & 761095 and in at least final Fluvirin release lot #E12821MA, For initial batch record 759931 with indications on page #1 of re-filtration into batch # 760136 and documentation of bioburden levels test results before and after lot was re-filtered, see **(Exhibit #OOOC1, page #7-9.** For the use of this lot in the trivalent formulation lots761025 & 761095 that were eventually released into US market, see **Exhibit #OOO1C2 & 1C3, 1F, & 1G).**

For a list of OOS monovalent flu lots that were re-filtered and further manufactured into trivalent lots and distributed into USA and Rest of the world, see **Exhibit #OOO1D**. It should be noted that monovalent lots that were further manufactured into trivalent lots and distributed in the USA/Rest of World were designed as such by Dr. Pawson in red pen.

For a list of monovalent lots that were re-worked/re-filtered provided by Dr. Pawson, see **Exhibit #OOO1E**. It should be noted that not all of the listed re-worked monovalent lots that were manufactured into trivalent batches were distributed in the USA.

For listing of monovalent/monoblend lots and the newly re-assigned lot number after re-filtration for year 2001/2002 including the final/finished Fluvirin vial lots that the monvalent lots with high bioburden levels were used and referred to on the list as "Pack Lot", see **Exhibit #OOO1F & 1G.**

For a list of manufactured rejected trivalent lots, see **Exhibit #OOO1H**.
For listing of all trivalent bulk/vials flu vaccine distributed in the USA for the year 2001/2002 with indications of re-filtered lots by Dr. Pawson, see **Exhibit #OOO1J &1K.**

For SOP #SP155 dated April 19th 2003, titled: General Procedure for Performing Rework Operations in all Areas, see **Exhibit #OOO1M.**

Pre Mr. O'Brien and Dr. Pawson, the firm's rationale for releasing monovalent lots with high levels of bioburden after it meets the bioburden specification of <---- cfu after re-filtration was based on---------- validation of microbial retention of the ----------µ---------- filter, **(Exhibit #OOO1N).** Per Mr. O'Brien/Dr. Pawson and as stated in the investigation report conclusions of the monovalent lots with high bioburden levels: the monovalent lots were successfully filtered because of the bacteria retention capacity of ------ and ---------- total surface volume of the sterilizing filter used. According to Mr. O'Brien and Dr. Pawson, the filtered lots bioburden levels were within the validated limits of the filter's retention capability of ---------- for bioburden, **(Exhibit #OOO1A1, page #8 & 12-15, 1B1-3 page #8-10 & 1C1-3 page #7-9).**

D.) There is no procedure that requires stability assessment of re-filtered batches, including SOP BLE024 Fluvirin Reprocessing at Monovalent and Trivalent Blend Stage (Ex R-1). The only stability study that included re-filtered batches, R/0184/07/00 (Ex R-2) dated August 1, 2000, was not designed as refiltration protocol and assessed only previous monovalent strains, rather than those currently processed. The study also only assessed one syringe and one vial lot in one monovalent strain. The Stability Report does not include volume refiltered or pre-filtration bioburden. There is no protocol for assessment of stability of re-filtered Fluvirin when the monovalent strains change from season to season.

R-1 SOP BLE024 Fluvirin Reprocessing at Monovalent and Trivalent Blend Stage
R-2 Protocol R/0184/07/00

(RWJ)
Concerns expressed by Investigator Osunsanmi, reported as observations 1a-c, resulted in a reply by Simon Bryson that the firm had stability data to support re-filtered Fluvirin. The data supplied by the firm was the study R/0184/07/00 which John O'Brien stated was the only stability data the firm had generated for re-filtration.

Discussion with O'Brien revealed that the study was a routine stability program performed in 1999 that happened to include 2 lots that were re-filtered-the protocol was not designed as a validation protocol for re-filtration.

Current stability data for re-filtration does not fully support the process and there are no considerations for product changes from season to season.

We discussed the possibility of designing a protocol to place the next series of re-filtered lots on stability and obtaining concurrence from CBER. Firm reps stated that no re-filtered lots would be distributed prior to submission of a CBE-30 to CBER with stability data.

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2) Control and failure investigations into bulk Fluvirin monovalent blends/lots at ---------- step with high levels of bioburden is deficient, in that lots were noted with total volume of high bioburden levels of e.g., $9.66x10^6$ cfu, $7.07x10^7$ cfu & 1.26×10^7 cfu in year 2000/2001 and 2001/2002 campaigns and no formal investigations has been opened to find the root cause of the high levels of bioburden in these lots.

(OOO)
The inspection noted that the firm has been experiencing high levels of bioburden since year 2000 per previous inspection reports and this inspection. The review of the bioburden levels non-conformances noted that in most instances failure investigations were conducted into individual occurrences. The noted preventive action-to prevent reoccurrence of non-compliance indicated on the Non-conformance Investigation Report Form included in SOP #SCP009 dated September 9th 2002 revealed the following notations on at least three collected non-conformance reports: "Not Applicable", "None" & 'None', **(Exhibit #OOO1A1 page #3, 1B1 page #3 & 1C1 page #3).**

The inspection noted that on the individual non-conformance reports that were review no attempts were made by the firm to investigate the root cause of the higher than expected bioburden levels. In addition, there was no documentation that the firm opened a formal investigation into the high levels of bioburden levels to find the root cause and eliminate the potential source/sources of the contaminations. For SOP #SCP009 dated 9/9/02 titled: Non-conformance Investigations, see **Exhibit #OOO2A.**

3) There is no documentation that the decisions to continue with the manufacturing of the Fluvirin monovalent lots with high levels of bioburden levels were based on the pathogenicity of the organisms that were isolated from the sampled lots, e.g., gram negative: *Serratia marcesens, Enterobacter cloacea*, and *Pseudomonas putida.*

The review of high bioburden Fluvirin lots and justifications for the release of these lots revealed that decisions to release lots with high bioburden levels for further manufacturing into trivalent lots were not based on the review of the pathogenicity of the organisms identified. Although the organisms in the sampled lots were isolated and identified, and the results of the sampled re-filtered lots were within bioburden specification of ------ cfu however, the decision to release the monvalent lots for further manufacturing failed to include the review of the identified organisms ability to cause serious illnesses and/or types and levels of toxicity production that could be harmful to humans, **Exhibit #OOO1A1-4, 1B1-3 &1C1-3.**

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4) Sterility failure investigations do not fully include all potential roots of contamination and corrective actions are incomplete. For example,

A.) The NCR investigations of Monovalent Blend Pool Batch #762492 refiltered into Batch #762835 dated July 2002 (Ex R-3) and batch # 761650 dated May 2002 (Ex R-4) implicated aseptic connections as potential root causes but failed to result in procedural requirements for environmental monitoring during all aseptic connections and evaluation of possible reductions in the number of aseptic connections.

R-3 NCR 2002/618/07 lot # 762492
R-4 NCR 2002/163/07 lot # 761650
R-5 NCR SOP SCP009

Note: Monovalent batch # 762492 was re-filtered into batch # 762635 (not batch #762835).

(RWJ)
The QA investigation for NCR 2002/618/07 for batch # 762492, page 4/5 for Manufacturing Areas states "there is a possibility that the monovalent blend pools could have become contaminated during aseptic connections." The NCR Conclusion, page 5, states "the most likely source of the contamination is from aseptic connections within then Formulation area." Corrective actions were reported as only maintenance of aseptic operator's gowning and aseptic procedure qualifications. There was no discussion of aseptic connection procedures or monitoring.

The QA investigation for NCR 2002/163/07 for batch #761650 reports two possible routes of contamination, rotors during centrifugation and operators during formulation. The Actions section states to "review the applicability of reducing the number of aseptic connections during the filtration process." There is no evidence in the NCR of corrective actions taken or studied.

There was little evidence that corrective actions were investigated for sterility failure investigations in NCRs reviewed.

The NCR SOP SCP009 states that is the responsibility of the appropriate Manager and QA Manager to follow-up any corrective and preventive actions raised. The SOP, sections 7.16-7.20, includes CAPA instructions. However, there are no specific instructions that detail how proposed corrective actions will be discussed, implemented (or not) and closed in NCR reports.

B.) Settling plates were placed on the formulation tank at least 15 minutes after aseptic connections to the tank during the formulation of New Caledonia lot # 764984 observed on June 4, 2003. Active viable and non-viable monitoring was initiated at least one hour after all connections were made including those to the---------- unit which are made in Class ----------conditions ---------- .

R-6 Manufacturing Instruction lot# 764984

(RWJ)
I observed the set-up for Monovalent formulation of New Cal lot# 763984. There was no monitoring during the aseptic connection process. Previous investigations implicating aseptic connections in bioburden and sterility failures did not result in monitoring of connections.

C.) Klebsiella oxytoca was isolated in the Centrifugation -------batch 762450 and the ---------- Zonal Concentrate batch #762451 that went into batch #762492. K. oxytoca was also isolated in the---------- filtration sample as well as the sterile-filtered sample. There was no investigation of water monitoring results or environmental monitoring results prior to this batch.

(RWJ)
NCR 2002/618/07 (Ex R-3) reported the information cited. In addition to the lack of investigations of previous EM results and water monitoring, sterile filtration validation, cleaning validation and additional potential routes of contamination by equipment, cleaning agents and personnel were not investigated.

Concerns were expressed that the organism was repeatedly isolated throughout the process, even after the sterile filtration process.

Firm reps had no explanation for these occurrences but pointed out that this had not occurred regularly.

D.) From February 28 2002 to July 5, 2002, 14 ---------- Monovalent Blend Pools failed bioburden testing with a Klebsiella isolate. Closure of the sterility failure investigation of lot# 762635 (refiltered from lot# 762492) on July 9, 2002 did not include reference to nor investigation of the additional failed batches with the same isolate.

R-7 ---------- Isolates 2002 and 2001

(RWJ)

Again, NCR 2002/618/07 (Ex R-3) is the investigation cited. The number of contaminated ---------- lots is less than 10% of lots processed. However, ongoing issues with the ---------- system have been reported in both previous and current inspections. The firm reviewed the possibility of changing to a different ---- system but was still using the ---------- during the current inspection with the historical cleaning procedure. Review of the contaminated batch microbial isolate data also demonstrated 14 batches contaminated with Serratia spp. from March 2001 to July 2002. Several additional batches were contaminated with Enterobacter spp.

Although firm quality reps stated that the contamination issues were repeatedly discussed at meetings, there was no summary investigation report of the issues.

E.) There was incomplete review and approval justification for retests in sterility OOS test results reviewed for 2001 and 2002.

R-8 Log of sterility OOS results 2001-2002
R-9 M198 Sterility Investigation Reports
R-10 M001 Sterility Testing
R-11 SIR 02/002 batch #761650 2/02

(RWJ)
There were no sterility failures for filled vials. Failures occurred at the monovalent blend pool stage, including after sterile filtration, however:

Procedures for investigation of sterility failures including M198, Ex R-9, and M001 Sterility Testing, do not provide clear instructions for the initiation of retest after an initial test reported contamination.

For example, the Sterility Investigation Report SIR 02/002 for Batch # 761650 in February 2002 simply reported that an initial test failed and a retest was performed. There was no justification for the retest and results were reported as valid.

Simon Bryson stated that improved sterility investigations were a priority upon his arrival at the firm in 2002. It appeared that investigations had improved in completeness in 2003.

5) The following deficiencies were noted in product contact equipment compatibility:

A) There is no filter compatibility and extractable validation studies on filtered Fluvirin monovalent and/or trivalent bulks. In addition, filter compatibility was not considered in the product stability failure

investigations. As such, filter compatibility studies has not been eliminated as the reason for loss of potency after the trivalent filtration step that resulted in failures of four out of five Fluvirin lots placed on stability for year 2001/2002 campaign.

B) The---------- used throughout the Fluvirin manufacture process to transfer centrifuged, formulated and finished product for filling was out of specification of --- mg for USP Non-Volatile Residue with result of 1327 mg per ----------test result. No investigation, corrective and preventive action has been conducted and no justification/rationale is provided for lack of investigation.

(OOO)
The review of the cGMP FDA-483 dated March 2001 revealed that the following Observation #28 was cited:

> *"There was no testing performed to determine the compatibility of the final vaccine formulations with the manufacturing equipment".*

Also, the Pre-approval Inspection of May 11th 2001 cited Observation #11 as follows:

> *"There were no extractable studies performed on--------- tubing used in the filling of the product".*

The inspection revealed the firm's failure to conduct comprehensive review of its operations in relation to previously cited observations to assure adequate corrective actions. For example, the firm failed to include the filter compatibility/extractable studies in its corrective action to the above observations noted during the Pre-approval/cGMP inspections. The review of the filter compatibility and extractable studies disclosed that the firm has not conducted compatibility and extractable studies for the ---------- ----- µ------ ---------- filter. The filter is used in the filtration of the monovalent lots and the final aseptic filling of the trivalent lots. Dr. Pawson and Mr. O'Brien agreed with the observation and promised corrective actions.

The inspection noted that the firm conducted corrective action to the May 2001 PAI observation. However, deficiencies in the corrective action were noted as discussed in Observation #5B above. The inspection also noted that the ---------- ---------- Tubing used throughout the Fluvirin manufacture process to transfer centrifuged, formulated, and finished products for filling was out of specification of --- mg for USP Non-Volatile Residue with result of 1327 mg per---------- test result, **(Exhibit #OOO5B page #3)**. However, no investigation, corrective and preventive action has been conducted and no justification/rationale is provided for the lack of investigation. I

informed Mr. O'Brien that after the tubing test result was OOS for USP specification of ---mg for Non-Volatile Residue with results of 1327mg that the firm should have provided documented justification for the continued use of the ---------- tubing as well as future planned corrective action. Furthermore, I suggested to Mr. O'Brien that the firm could show through documented studies that the level of the ---------- tubing non-volatile residue is within acceptable level in the monovalent/final product.

Per Mr. O'Brien, the firm is currently testing other tubing with Fluvirin to determine compatibility. Mr. O'Brien also promised corrective action to the observation.

6) The investigation into the reported Fluvirin potency stability test failures in 2001/2002 and 2002/2003 was incomplete. For example,

R-12 Summary Report Investigation into Fluvirin Stability Results

(RL/JM/RWJ)

A.) The conclusion implicating CBER reagents in the test failures was not fully justified. The study did not address that failures primarily occurred only after 6 months on stability. Root cause(s) have not yet been identified, including potential contributing factors specific to the antigen and antiserum and the investigation is ongoing.

This observation was made by Jonathan McInnis and written by Robert W. Jennings

(JM)
Evans presented for review a summary of experiments performed to investigate the problem of loss of potency in the New Caledonia (H1) component of their trivalent vaccine in both the 01-02 and 02-03 flu seasons.

The summary also included test results and information regarding ---------- levels found in some the lots failing stability. The summary appears to fully address the ---issue, presenting an outline of their experimental approach and providing supporting data. Evans has theorized that ---------- from the ---------- in the Ready-ject Syringe (RS) presentation of the vaccine in the form of ----- ---------- is reacting with components of the vaccine to produce ---------- ---------- causing a ----------. Based on the results from these studies, Evans is ---------- ---------- ---------- for the upcoming flu campaign.

The summary, however, does an inadequate job of addressing the loss of potency issue. Evans theorizes that a problem with reagents from CBER, namely the reference antigen, is causing the potency of the H1 component of their trivalent to appear subpotent. A

matrix type study was conducted wherein reagents from CBER are compared with reagents from National Institute for Biological Standards and Control (NIBSC) using several different reagent combinations, **(Exhibit R-12, page# 11)**. The study does demonstrate that differences do exist between the reagents but the implication that the CBER reference antigen is the causative agent is not supported as the study can not identify which of the reagents is responsible for the differences.

These issues were discussed with Evans and during a presentation to the inspectors, Evans has acknowledged that they are unable to identify the root cause and that they will formulate their trivalent bulks with a higher H1 concentration to assure that they remain at or above the potency specification throughout the dating period.

(RWJ)
The investigation Summary Report states that "there is currently no explanation for the differences in potency results obtained using reagents from CBER, NIBSC and TGA-consideration is being given to further investigative work on this issue at the molecular level. "

B.) The manufacturing investigation did not include a failed 2000/2001 batch and 2001/2002 batches reviewed were not fully identified in the report (Appendix 14). The root cause investigation was not included in the report.

R-13 Appendix 14 of the Fluvirin stability investigation
R-14 BPDR summary table

(RWJ)
There is no identification of the full scope of 2001/2002 batches reviewed in the report. A 2000/2001 pH failure for lot# E59230GA, reported in a BPDR summary table (Ex R-14) was not included.

According to the firm representatives, an extensive root cause investigation was performed. There was no evidence of the investigation in the investigation report.

C.) There was no review and approval of the Summary Report Investigation into Fluvirin Stability Results by management involved in the investigation. The Summary Report is not dated.

Ex R-12 is the summary report. It is not signed nor dated.

D.) There was no review and approval of the draft Clinical Expert Report dated September 4, 2002 justifying the firm's decision not to execute product recall. The author of the report is not identified and did not sign the report.

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R-15 Clinical Expert Report draft dated September 4 2002

Ex R-15 is the draft Clinical Expert Report. It is not signed nor dated and the author is not identified in the report. Additionally, there is no evidence a final report was generated, signed, reviewed and approved by QA.

The conclusion of the Clinical Expert Report, after repeated stability failures for ph and potency for Fluvirin, states that "the available data does not suggest any significant drop-off in immunogenic for HA content in the range of ----------ug/ml. In particular, the A/New Caledonia strain used in the Fluvirin 2002/2003 formulation has been tested at concentrations as low as ----- ug/ml with a good retention of immunogenicity."

7) The Biological Product Deviation (BPDR) reported June 28, 2002 for reported Fluvirin potency and pH stability test failures was incomplete and failed to provide FDA significant information for timely evaluation. Additionally, there is no justification for management's failure to identify the significance of failing and missing test results during review and approval of the results and the ongoing stability program as required by Stability Policy Document SCP041. For example,

R-16 BPDR submitted June 28, 2002
R-16A Stability Policy Document SCP041

(RWJ/JM/RL)
This observation was made and written by Robin Levis, Jonathan McInnis and Robert Jennings.

(RWJ)
The concerns expressed in this observation and related discussions included the failure to submit information necessary for timely FDA review. In particular, the limitations of the BPDR reporting requirements (45 days), combined with the limited shelf-life of Influenza vaccine and the further limited use period, usually less than 6 months, was discussed. It was pointed out to the firm the importance of early and timely reporting of potential issues. In the case cited, the first and really only potency failure information that was likely to impact current supplies and the current flu season, was not reported to FDA. Additional information was not reported. Management was encouraged to discuss these issues verbally with CBER product specialists as soon as they arose and management agreed.

(JM)
As a subpoint to the stability failures, review of the Evans 2001 Annual Report revealed that during the 2000-2001 flu season several stability test time points were missed for multiple batches (E12201MA-no data for months 1,2,3 or 6; 759881-no 1 month data;

759819 and 759872-no 2 month data). Considering the problems with failed stability lots and the sparse number of lots in the program, it is notable that some testing was not conducted as required. When asked why the tests were not conducted the Evans' response was that they were simply overlooked. It was recommended that Evans be more diligent in this area in the future and also to add more lots to their stability program.

A.) The firm simply reported that OOS potency and pH test results had occurred and no failing test results, including failing New Caledonia potency test results and stability test time points (specification minimum --- mcg HA per SRID), were submitted.

R-17 Table 1 Fluvirin Stability pH and SRD data (2001/2, 2002/3)

(JM/RL/RWJ)
The BPDR did not include specific test results and none were submitted via follow-up reports. Ex R-14 is a summary of data pertinent to the BPDR that was not submitted. similar presentation is Table 1 Fluvirin pH and SRD A/New Caledonia stability data Ex R-17. At least 5 lots failed SRD in 2002/3 on stability.

B.) Although the firm reported that a failure had occurred for lot# E00931HA, they did not report that the initial failure of the 2001/2002 season (26.8 mcg) occurred at the scheduled 6-mo test point reported February 10 2002, over 5 months prior to BPDR submission. The lot also failed at the 9-mo test point (24.9 mcg) in May 2002 and the 12-mo test point (13.1 mcg). The firm did not have a rounding procedure and reportedly did not consider 26.8 mcg a failure-no report to FDA was made for the 6-mo result.

R-18 Stability Report for lot# E00931HA

(RWJ)
Ex R-17 shows the failure of lot# E00931HA at the 6-month time-point. This was not included in the BPDR summary document prepared for this inspection. Per John O'Brien and Lisa Bissett, Stability Manager, 26.8ug was not considered a failure. However, the firm had no rounding procedure and there is no documentation that the test result was reviewed and dispositioned a pass. Per the firm reps, the result would now be considered a failure.

However, the stability report for lot#E00931HA states in the Discussion section, page 7, the SRD assay at the 6, 9, 12 and 13-month time points for A/New Caledonia did not comply with the specification at these time points. The stability report references the reported BPDRs in June and September 2002 but fails to explain the exclusion of the failure at the 6-month time point.

SCP041 Stability Policy requires reporting and evaluation of all results and missed time points.

C.) No information was submitted to FDA on lot #s E12201MA (24.1 mcg) and E11371LA (21.9 mcg) which failed when first tested on stability at the 7-mo test point on May 26, 2002. Required tests at the 1, 2, 3 and 6-month time points were not executed-this was not reported to FDA. No NCR was initiated for missed time points and failure to submit BPDRs and no justifications have been written. Limited data on these lots were submitted without full explanation in the related September 4, 2002 BPDR. Shelf-life Stability Summary Reports for the two lots, reviewed and approved by QA, QC and RA in January 2003, failed to report and evaluate missed time points in the studies.

(RWJ)
Ex R-17 shows the missed time points as (-) dashes. The additional data is also presented for lot #s E11371LA and E12201MA which both failed at 7-months in May 2002. The information is included in the specific stability reports for these lots, Exs. R-19 and R-20.This information was not included in the June report but was included in a follow-up BPDR report in September (Ex R-21), only on a limited basis.

R-19 Stability Report Lot# E11371LA
R-20 Stability Report Lot#E12201MA
R-21 BPDR September 4, 2002

8) No BPDR was submitted for the Fluvirin pH OOS (7.9) at the 3-month test point on December 18, 2002 for lot # E34652KA 2002/2003 season. A follow-up report to the September 4, 2002 BPDR was not submitted in which the firm reported that additional OOS pH results were likely to occur in other batches.

(RWJ)
Ex R16 shows the failure of Fluvirin pH on stability for lot#E34652KA at the 3-month time point in December 2002. Firm reps stated that they did not consider it necessary to report additional failures once a BPDR had been submitted indicating that additional failures were likely.

I stated the firm was expected to submit a detailed follow-up report appending data to the original report.

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9) Corrective action has not been implemented for the previous FDA 483 observation regarding the failed ---------- System cleaning validation study CVR/0016/00 dated August 16, 2000. For example,

A.) The firm's response to the previous FDA 483 stated the evaluation of the study concluded there was no impact on Fluvirin. From March 2001 through 2002 at least 30 ---------- Monovalent Blend Pool lots failed bioburden testing.

R-22 Response to Inspectional Observations issued on March 9, 2001

(RWJ)
The observation reported that the cleaning validation did not meet acceptance criteria and the response stated that their evaluation "concluded that there is no impact upon the quality, potency and safety of the Fluvirin processed by the ----------." The response also stated that a draft protocol for Cleaning of the---------- System was attached. The ---------- system was never implemented.

As discussed above in observations 2 and 4, bioburden issues have repeatedly arisen ---------- - . The firm has failed to fully correct these issues.

B.) Validation protocol for the executed study CVP/0011/03 dated April 7, 2003 (Ex R-23), changing the sanitizing agent to ---------- ---------- , did not include bioburden reduction by assessing microbial load prior to use or storage between use.

(RWJ)
The firm decided to execute an additional cleaning validation study on the----------, CVP/0011/03, Ex R-23 and attempt to validate cleaning with ---------- The firm simply executed a study under routine use but there is no information on pre-load bioburden or storage conditions between uses.

C.) Design and operation of the---------- filtration unit located in the Formulation area allows operator error to potentially reverse the flow of product under filtration. The---------- has a piece of masking tape over the flow direction dial on which is written "Do Not Use". Use of the flow director would reverse the flow of product. The dial is located next to another dial that requires regular use for pressure regulation.

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R-24 BLE022 Operation of---------- System

(RWJ)
This condition was noted during observation of formulation operations. The tape is not included in the SOP for operation of the ----------. This condition was reportedly corrected during the inspection and training was pending.

10) It was noted during the observation of formulation of A/New Caledonia Monovalent Blend Pool batch # 764983 on June 4, 2003 that sub-batch ---------- samples were not taken as required (per SOP ZY033A Release of ---------- Concentrate to the Formulation Department including the - -day ruling) ----- days after the ---------- ------ centrifugation run on May 22, 2003. There are no procedures to assure samples are taken and there is no information this deviation had ever been previously identified. The NCR investigation to determine additional batches affected by similar deviations was reportedly ongoing.
Note: The batch # observed was 764983 not 764984.

R-25 Partial batch record for New Caledonia lot# 764983 blending
R-26 Release of ---------- Concentrate to the Formulation Department including--- day ruling.

(RWJ)
During the observation of formulation of New Caledonia lot# 764983 blending on June 4, 2003 I asked the procedure for monitoring endotoxin during ---------- - batches. The firm has an SOP for Release of the ----------Concentrate to the Formulation Department including - -day ruling, Ex R-26, which requires - ---------- sampling and testing every - days (section 7.8 of the SOP). These samples were not executed for lot# 764983 prior to blending. There was no procedure to assure the samples were taken prior to formulation.

The firm had initiated an investigation to determine if additional batches were implicated in this oversight as well as SOP revisions after this observation and before the closeout of the inspection.

11) The following was noted during vial filling on June 6, 2003 (under Protocol P/0097/04/03):

R-27 P/0097/04/03 Filling Instructions for Filling of Fluvirin containing different preservatives

A) There was no documentation in the batch record of missed stoppers or seals and there is no procedural requirement to do so.

(RWJ)
This observation applies to both routine filling, and media fills. I noted missed stoppers and seals on the turntable. They are not documented.

B) A panel, about 8 by 10 inches, was open in the cabinet under the filling machine and there was no information on the length of time this condition had existed or that correction had been scheduled. The open panel area could allow the accumulation of potential contaminates under the filling machine that would be difficult to clean/sanitize.

(RWJ)
Filling on June 6, 2003 was the first filling on the Fluvirin line for the 2003/2004 campaign. The open panel remained from the maintenance period. However, there was no information as to whether it may have been open last year or would have been corrected without the observation.

C) An operator was noted to be pushing curtains into the area near open empty vials while retrieving tipping vials on 2 occasions disrupting vertical laminar flow.

(RWJ)
In order to retrieve tipped vials it is necessary for an operator to enter an arm into the LFU. With the current design of the LFU unit, an improved practice would be to breach the laminar flow through the curtains without pushing the curtains into the LFU, if possible. If this proved difficult, another possibility would be to redesign the barriers and place plexi-glass "Perspex" in the U.K., on the unit. This was discussed with the firm reps.

D) 2 plastic yellow beakers used for holding forceps were scratched and yellowed.

(RWJ)
This observation was reportedly corrected during the inspection although preventive training had not been executed.

12) Regarding sanitizer efficacy validation study protocols,

A.) Study R/0083/05/01 Evaluation of Disinfectant Products using Qualitative European Surface Tests for both Bacteria and Fungi dated July 13, 2001 failed to include the full range of cleaning agents (i.e.----------) and manufacturing surfaces (i.e. laminate on doors, Perspex on filling unit curtains). Additional

studies, i.e. PQP/0026/01, did not assess cleaning efficacy on manufacturing surfaces.

R-28 R/0083/05/01 Evaluation of Disinfectant Products using Qualitative European Surface Tests for both Bacteria and Fungi
R-29 SCP017 Approved Cleaning and Disinfectant Agents

(RWJ)
The combined sanitizer efficacy studies failed to address all the cleaners used in current SOPS, i.e. SCP017 Approved Cleaning and Disinfectant Agents, Preparation of Working Strength Solution and Rotation Policy, Ex R-29 and materials noted during tour of the filling and preparation-for-filling areas.

B.) Acceptance criteria were not met for Study R/0083/05/01 against bacteria including spore-formers and mold and no additional protocols have been written/executed.

(RWJ)
The conclusion of the study is that "although ---------- and----------did not achieve minimum requirements....the activity achieved would be sufficient to effectively "kill" the resident microbial population, with the exception of *Bacillus licheniformis and Aspergillus versicolor.* "

The firm reportedly planned additional studies.

13) No protocol deviation was initiated for the failure to execute the portion of Protocol PVR/0005/01 Determination of effects of Holding Times on the potency of Fluvirin Monoblend Pools, requiring that a routine batch be placed on stability. The summary report, reviewed and approved by QA on January 30, 2003, reported that the routine batch was not placed on stability while also stating that no differences between the test batch and routine batch were observed. Another protocol was not executed.

This observation was made by Robin Levis (RL) and written by Robert W. Jennings. (RWJ).

R-30 Protocol PVP/0005/01 Determination of the effects of Maximum Holding times on the potency of Fluvirin April 2001
R-31 Report PVR/0005/01 dated January 2003
R-32 SOP VAL002 Executing Validation Protocols

(RWJ)
The firm's procedure for validation studies VAL002 states that in the event an error is found in a protocol a Validation Comment Form must be completed (Section 7.9.3.) Firm reps stated this procedure was not followed but is intended to include protocol deviations during execution in addition to significant issues identified in protocols themselves. The written procedure does not explicitly state that Comment Forms also apply to protocol deviations

(RL)
In addition to not including a protocol deviation report, the process validation report, R-31 PVR/0005/01 dated January 2003, is misleading in that the discussion of results obtained did not take into consideration that data is missing from the final analysis. The firm stated that the scope of report discussions will be expanded to include deviations and all events which influence the outcome of the study.

14) Regarding Batch records including review, approval and batch release,

A.) Procedures do not assure full review of deviations prior to release. Worksheets to assure QA batch record review and product release are not included in written procedures, i.e. QA Bulk Trivalent Checklist Ex R-33 (not in SOP QASP093 QA Procedure for Review of Finished Product, Ex R-34) and Fluvirin Trivalent Vaccine Product Release Checklist Ex R-35(not in SOP PRG020 Release of Finished Products from Quarantine Ex R-36), i.e. Trivalent batch # 762834, filling batch #762925 and Packing batch #E31192HA released September 4, 2002.

R-37 Product Release Checklist for Packing lot E31192HA dated September 4, 2002.

(RWJ)
Review of the firm's release procedures revealed a lack of assurance that all deviations were reviewed prior to batch release. Worksheets for bulk and finished product release were not included in written release procedures. Only three batches were briefly reviewed for identification and review of deviations prior to release.

B.) An incorrect NCR was referenced in the batch record for the sterility test for batch # 762834.

R-38 Corrected sterility test NCR in the batch record for lot# 762834

(RWJ)
QA reps corrected the sterility test document on June 9, 2003 by crossing out the incorrect NCR referenced (2002/969/03) and documenting the correct NCR 2002/1052/02.

The incorrect NCR was reported by QC and not identified by QA during batch review.

C.) Labels for working seed cell culture vials are not maintained in the Manufacturing Instruction batch records, i.e. B/Hong Kong/330/01 lot# --------- Evans - ¯ passage dated October 25, 2002.

R-39 Batch Record -------- dated 10/25/02
R-40 MI0350 Passage of Influenza Seed Material

(RWJ)
The firm labeled the passaged working seed vials but the labels were not put into the batch records. The Manufacturing Instruction MI0350 does not require it.

D.) There was no documentation in the filling batch record of a leak in filling tubing causing the filling process to abort for lot# 762838 on June 6, 2002. Although an NCR was initiated, there is no evidence in the batch record the leak occurred.

This observation was made by Robin Levis and written by Robert W. Jennings (RWJ).

R-41 NCR/827/02 dated September 5, 2002
R-42 Filling batch record, selected pages, lot# 762838 June 7, 2002.

(RWJ)
The firm initiated an NCR, Ex R-41, for a leak during filling that required aborting of the fill. The batch record for lot# 762838 did not report the incident. The NCR was closed 3 months after the incident.

15) There is no requirement for investigation of consecutive, repeated alert level sample results for water monitoring as allowed by SOP M154 Water Monitoring Excursion Reports.

R-43 M154 Water Monitoring Excursion Reports

(RWJ)
The firm proposed to correct this deficiency by establishing a sampling rationale for alerts. The SOP M154 has no requirements for investigation of repeated alerts.

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16) The following deficiencies were noted in the Fluvirin media fill simulations:

A) Media fill simulations are not representative of actual aseptic filling process in that interventions that occurred during aseptic filling processes are not evaluated and considered for incorporation into media fill simulations.

B) Worst case conditions to be conducted during media fill simulations are not defined in SOP # SCP029 dated 9/9/02: General Procedure for Routine Monitoring of Aseptic Manufacturing Processes by Process Simulation Utilizing Sterile Media Fills and/or Performance Qualification Protocol # PQP/0067/01.

(OOO)
The review of the Fluvirin media fill simulations disclosed that from year 2001 to 2002 the firm had no media fill failures, **(Exhibit #OOO16A1).** However, the review of the media fills/aseptic fills batch records disclosed no assurances that media fill simulations are representative of routine aseptic filling processes. In addition, there are no documentation in the media fill batch records that interventions, which occurred during routine aseptic filling processes were incorporated into the media fill simulations, **(Exhibit #OOO16A2 & 16A3)**. In addition, it was noted that SOP #SCP029 dated September 9th 2002 tilted: General Procedure for Routine Monitoring of Aseptic Manufacturing Process Simulation Utilizing Sterile Media fills, failed to include the requirement to simulate interventions that occurred during aseptic filling processes. Furthermore, it was noted that SOP # SCP029 dated 9/9/02 failed to require or specifically state/define the simulation of worst case conditions that are to be conducted during media fill simulations, **(Exhibit #OOO16B).**

17) There was no documentation that adverse events (AE) reported for vaccine season 2002/2003 with the same lot numbers reported by different Health personnel/facilities on Fluvirin batches were reviewed, evaluated and/or investigated to determine if the adverse event may be related to the manufacturing process, for example:

A) Ten adverse events reported for batch #E35732HA on injection sites inflammation by eight different healthcare facilities.

B) Five adverse events reported on batch #E33922HA on injection sites inflammation by five different healthcare facilities.

C) Forty one adverse events reported on batch #E33402HA on injection site reactions reported by two healthcare facilities.

(OOO)
The review the adverse event files with Ms. Vivian Pearce-Higgins, Manager Pharma-co-vigilance in the presence of Mr. Jim C. Williams, Vice President of US Regulatory Affairs, disclosed that all adverse events were reported to FDA within the allowable time frames. Further review of the adverse event files revealed the above noted observations and the firm's failure to review the implicated lots manufacturing deviation reports/failure investigations to assure that they were not related to the Fluvirin reported adverse events, **(Exhibit #OOO17A, 17B & 17C).** For a listing of adverse events for year 2001/2002 showing the number of reported adverse events/lot, see **Exhibit #OOO17D.**

The review of the firm's Adverse Events SOP #MA 4901 dated June 18th 2001 titled: Processing, reviewing and expedited reporting of adverse events for marketed products, revealed the SOP has no requirements for when manufacturing process investigations are to be conducted when several adverse events with similar lot numbers/different indications of adverse events are received from the same healthcare facility/doctor or when adverse events with the same lot number/similar reported adverse events are received from several healthcare facilities/doctors, **(Exhibit #OOO17E)**. During the inspection, draft corrections to the SOP to incorporate the above concerns regarding requirements for the review of manufacturing deviations/failure investigations was presented to me by Ms. Pearce-Higgins, **(Exhibit #OOO17F)**. Although no evidence of personnel training was presented the corrections to the Adverse Events SOP was found to be adequate.

18) Temperature mapping study has not been conducted for the --- ---------- degrees centigrade) freezer, Serial ---------- used in the storage of frozen master and working seeds used in the manufacture of Fluvirin. (Protocol # IOQP/0040/03 dated 5/19/03 for the qualification of the freezer is currently in place).

(OOO)
For Protocol # IOQP/0040/03 dated 5/19/03 for the qualification of the freezer, please see **Exhibit #OOO18A.**

19) The following deficiencies were noted in the 100% Fluvirin finished vials visual inspections:

A) The 100% visual inspection and re-inspection of finished Fluvirin vials defects are not based on acceptable statistical sampling plans and/or

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review of historical data but based on ------ reject/accept rate that was used to set the initial limits.

B) The 100% visual re-inspections of finished Fluvirin vials are not based on a tighter sampling plan but are conducted at the same accept/reject rate of ------ as the initial 100% visual inspections.

C) Critical and non-critical finished vials inspection defects are not defined In SOP #IN017.VI dated 9/13/01; General Procedure for Performing Re-examination in Manual and Semi Automatic Inspection. In addition, all vial defects are based on the same reject/accept rate of ------ for, e.g., appearance, particles, broken glass, empty vials, and seals.

D) There is no Quality Assurance control/verification and/or over site of the 100% finished vials inspection for defects that are performed by manufacturing.

(OOO)
The review of Fluvirin finished vials inspection closed that the 100% visual inspection and re-inspection of finished Fluvirin vials defects are not based on acceptable statistical sampling plans. It was noted that all of the defects, e.g., particles, glass, seals, broken glass, and vial product volume are all based on ------ reject/accept rate. Also, the inspection revealed that the reject/accept rate is not based on review of historical data but based on ------ reject/accept rate that was used to set the initial limits, **(Exhibit #OOO19A, page #3).** In addition, the inspection revealed that the 100% visual re-inspections of finished Fluvirin vials are not based on a tighter sampling plan but are conducted at the same accept/reject rate of ------ as the initial 100% visual inspections per SOP #IN017.VI dated 9/13/01; General Procedure for Performing Re-examination in Manual and Semi Automatic Inspection, **(Exhibit #OOO19A page 3-4).**

Furthermore, the inspection noted that critical and non-critical finished vials inspection defects are not defined In SOP #IN017.VI dated 9/13/01; General Procedure for Performing Re-examination in Manual and Semi Automatic Inspection, **(Exhibit #OOO19A page #3).**

The review of the firm's quality assurance control over the inspections of finished vials disclosed that there is no Quality Assurance control/verification and/or over site of the 100% finished vials inspection for defects that are performed by manufacturing. Mr. O'Brien promised corrective action to all of the finished Fluvirin vials inspectional observations cited above.

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20) SOP #IN018 dated 5/25/03 for the training of Fluvirin 100% finish vials inspection personnel is incomplete, in that it failed to include the length of training of personnel for finished Fluvirin vials defect inspections and the level of supervision of the trained personnel after training.

(OOO)
The review of SOP #IN018 dated 5/25/03, titled: Inspection Assessment disclosed the above noted Observation #20, **(Exhibit #OOO20A).** The review of the SOP and deficiencies were reviewed with Dr. Pawson and he promised corrective action to the observation.

DISCUSSION WITH MANAGEMENT:

The following verbal observations were reported by RWJ to management:

- Smoke study video observed for syringe filling line lacked, in some instances, a demonstration of vertical laminar from the filter face to the work surface. (It was recognized that this was difficult to demonstrate in this study due to the small areas in the filling cabinet.)
- Vial-filling area-torn ------ - curtain outside tank transfer room; one -------- curtain outside cabinet edge stopper bowl cabinet/filling cabinet interface-where non-viable monitoring line entered cabinet; station for check weights is located in Class -------- room outside the filling room requiring numerous (10+) trips into and out of the filling room during set-up and start-up operations.
- Supporting records were not attached to EM excursion reports, i.e. EMER/03/FORM 004
- Current Calibration/qualification status was not reported on critical equipment, i.e. LF Hoods

Observations made by Investigator Robert W. Jennings were discussed primarily with John O'Brien, Head of Technical Services and Simon Bryson, Head of Quality. Stability issues were also discussed with Lisa Bissett. There was general agreement regarding the reported facts of the observations and requirements for corrective actions. Firm representatives made a point of both expressing the firm's intent to correct cited deficiencies and also, where possible, to discuss proposals for correction and demonstrate early corrective actions, if applicable.

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The following verbal observations were reported by JM to Management:

Mislabeled samples sent to CBER

Each monovalent batch is tested for potency at CBER. Samples from Evans are sent to DPQC and subsequently forwarded to the CBER flu lab for potency assignment. This season and last, CBER flu lab received mislabeled samples (i.e. vials labeled as B/Hong Kong actually contained A/New Caledonia) from the firm. Review of the samples mislabeling documentation during this inspection revealed that no NCR was issued on the previous/last season mislabeled occurrence, but NCR was issued for this season occurrence. The review of the issued NCR disclosed it did not contain any information for corrective actions. Additionally, no formal procedure or SOP exists to describe how the sample is collected and checked for accuracy in labeling prior to shipment to CBER. It was recommended that a system be implemented to eliminate this type of error.

Refortification of lots

The inspection team recommends that lots that have been refortified by Evans have an indication on the protocols sent to CBER that a reworking has occurred on that particular batch. This information would be useful to have at CBER to investigate any lots that appear subpotent.

The following verbal observations were reported to management by RL:

- Review of OOS report # V/OOS/2001/033 showed that two copied data sheets contained in the OOS report had been altered after initial use. No explanations for these alterations were included in the OOS report. (The firm was able to explain the alterations and will update the way in which data sheets can be altered.)
- A general review of the OOS reporting system shows that since the CBER inspection held in 2001, the reporting of OOS results and follow-up investigations has gotten better. The nonconformance reporting (NCR) documents are much more thorough and inclusive of information than the OOS reports. (The firm has drafted a new SOP for generating OOS reports which will update the way these results and subsequent investigations are handled.)
- During inspection of the warehouse and cold storage ------- ° C) facilities many large, unmarked containers were present in the cold storage. These containers held retain samples from -------- left over from a previous arrangement. It was suggested to the firm that the containers be labeled as to the contents and to the expiration or end of hold time. (The firm stated that the samples would be either correctly labeled or disposed of.)

- Review of the process validation report for study POP073 to evaluate the maximum time allowed for holding product at intermediate stages showed that an error in study execution occurred. (See 483 observation #13.) Samples from the normally processed lot were not retained for stability testing. In addition to the observation sited, the error in sample retention led to the acceptance criteria for the study not being met and the validation failed. It was suggested that the firm requalify this assay or consider repeating this validation assay.
- Review of the stability program showed several areas that needed to be changed.
    - Lots selected for inclusion in the stability program are not selected on a random basis. It was suggested that a system be developed for selecting lots for stability testing that was unbiased. (The firm developed a lot selection method that was satisfactory.)
    - The stability data collected to date on the flu strain New Caledonia A suggest that this strain is less stable than other strains included in the vaccine. To ensure the potency of New Caledonia A in the product for this season, it was suggested that the firm increase the amount of this strain included in the product. (The firm agreed to add at least --- micrograms/dose [an increase of -----] of this strain.) In addition, it was suggested that stability surveillance on this strain be increased to include an additional lot put on stability early in the manufacturing campaign and additional testing of the product early in the shelf life. (The firm agreed to implement this additional testing.)

ATTACHMENTS:

1) FDA-483 dated 6/02/03 issued to, Mr. Andy Sneddon, Head of Manufacturing /Site Director Liverpool.

2) CBER Assignment dated 5/16/03

EXHIBIT #OOO:

A) List of firm's personnel present during the FDA-483 close out discussion
B) Interstate Records
C) Consultants used for Fluvirin
D) List of firm's personnel that assisted Investigator during the inspection
E) Firm's Annual Report for year 2002
F) Firm's Organizational Chart
G) Manufacturing building diagrams
H) Fluvirin Manufacturing Flow Charts

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I) No Exhibit
J) Fluvirin Product Insert
K) USA Fluvirin Distributors
1A1) Non-conformance Investigation Report for lot 760351
1A2) Quality Control/Protocol Checklist for batch #760688
1A3) Quality Control/Protocol Checklist for batch #760641
1A4) Quality Control/Protocol Checklist for batch #760640
1B1) Non-conformance Investigation Report for batch #759931
1B2) Quality Control/Protocol Checklist for batch #760843
1B3) Non-conformance Report for batch #762920
1C1) Non-conformance Investigation Report for batch #759864
1C2) Quality Control/Protocol Checklist for batch #761025
1C3) Quality Control/Protocol Checklist for batch #761095
1D) OOS log for Microbiology QC Laboratory for 2001/2002
1E) List of Manufactured Lots-Reworked
1F/1G) List of Monoblend/Re-filtered, Trivalent and Pack lot for year 2001/2002
1H) List of Manufactured Lots Rejects
1J) List of Trivalent Bulk Lots
1K) List of Released US Vials/Syringes
1L) SOP #BLE024
1M) SOP #SP155
1N) ---------- Validation Report of filter microbial retention
2A) SOP #SCP009
3) No Exhibit for observation #3
4) No Exhibit for observation 4
5B) Testing Results for ---------- ---------- Tubing
16A1) Broth Fill Summary for Year 2001/2002
16A2) Performance Qualification Protocol dated 6/4/01
16A3) Media Simulation Worksheet dated 2/6/03
16B) SOP #SCP029
17A-17C) Adverse Events report per batch
17D) List of Fluvirin Reported Adverse Events per batch
17E) SOP #MA 4901
17F) Draft Proposal for Revision to Adverse Event SOP
18A) Installation Operational Qualification Protocol
19A) SOP #IN017
20) SOP #IN018

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EXHIBITS (RWJ)

R-12 Summary Report Investigation into Fluvirin Stability Results
R-13 Appendix 14 of the Fluvirin stability investigation
R-14 BPDR summary table
R-15 Clinical Expert Report draft dated September 4 2002
R-16 BPDR submitted June 28, 2002
R-16A Stability Policy Document SCP041
R-17 Table 1 Fluvirin Stability pH and SRD data (2001/2, 2002/3)
R-18 Stability Report for lot# E00931HA
R-19 Stability Report Lot# E11371LA
R-20 Stability Report Lot#E12201MA
R-21 BPDR September 4, 2002
R-22 Response to Inspectional Observations issued on March 9, 2001
R-23 CVP/0011/03 dated April 7, 2003
R-24 BLE022 Operation of ---------- ---------- System
R-25 Partial batch record for New Caledonia lot# 764983 blending
R-26 Release of ---------- Concentrate to the Formulation Department including -- day ruling.
R-27 P/0097/04/03 Filling Instructions for Filling of Fluvirin containing different preservatives
R-28 R/0083/05/01 Evaluation of Disinfectant Products using Qualitative European Surface Tests for both Bacteria and Fungi
R-29 SCP017 Approved Cleaning and Disinfectant Agents
R-30 Protocol PVP/0005/01 Determination of the effects of Maximum Holding times on the potency of Fluvirin April 2001
R-31 Report PVR/0005/01 dated January 2003
R-32 SOP VAL002 Executing Validation Protocols
R-33 QA Bulk Trivalent Checklist
R-34 SOP QASP093 QA Procedure for Review of Finished Product
R-35 Fluvirin Trivalent Vaccine Product Release Checklist
R-36 SOP PRG020 Release of Finished Products from Quarantine
R-37 Product Release Checklist for Packing lot E31192HA dated September 4, 2002.
R-38 Corrected sterility test NCR in the batch record for lot# 762834
R-39 Batch Record--------- dated 10/25/02
R-40 MI0350 Passage of Influenza Seed Material
R-41 NCR/827/02 dated September 5, 2002
R-42 Filling batch record, selected pages, lot# 762838 June 7, 2002.
R-43 M154 Water Monitoring Excursion Reports

EVANS VACCINES

Rec'd Dcm 7/17/03 DSA

K. Midthun, M.D., Director
Office of Vaccines Research & Review, HFM-99
Center for Biologics Evaluation & Research
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448,
U.S.A.

June 27, 2003

Re: Team Biologics Inspection of Evans Vaccines Limited, Gaskill Road, Speke, Liverpool, L24 9GR, U.K., June 2-10, 2003
Response to Form FDA 483

Dear Dr. Midthun

Evans Vaccines is providing responses to observations issued in Form FDA483 on June 10, 2003 by Team Biologics Investigators, Mrs. Omotunde Osunsanmi and Dr. Robert W. Jennings, and CBER Investigators, Dr. Robin Levis and Mr. Jonathan McInnis, during the inspection at Evans Vaccines Limited, Gaskill Road, Speke, Liverpool, L24 9GR, U.K. (BL 1615).

The responses to the observations in Form FDA 483 are presented in the following manner:

Observation: Observation number and Observation, as set in Form FDA 483.
Response: A response to the observation. Within each response Evans Vaccines provides corrective and preventative actions and a commitment date.

Evans Vaccines will provide quarterly status reports on activities to meet our quality commitments.

Evans Vaccines would like to meet with the agency as soon as possible to review Evans Vaccines' global and systemic approach. At this meeting we would welcome the opportunity to present to the agency our Quality Systems Improvements Program.

Evans Vaccines is committed to continuous quality system improvements. In May 2003 Evans Vaccines launched an enhanced program in support of our existing quality system improvement plan. Quality systems improvements will be addressed on a global basis to assure consistency in the applications of cGMPs across the manufacturing sites program will be an ongoing global initiative for the company.

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A PowderJect Company
Oxford & Speke UK Pleasant CA & Madison WI & Parsippany NJ USA

Quality System Improvement Program (QSIP)

As part of Evans Vaccines' commitment to continuous quality improvement, we recognize our responsibility with respect to understanding any gaps and required improvements in our quality systems. We achieve this level of understanding of our quality systems through a proactive review of our systems and processes, and effective involvement and participation on quality improvements at all levels throughout the organization.

We have recognized some areas within our existing operations, which require improvement. The high priority quality system elements have been incorporated into the Liverpool site quality objectives for the financial year April 2003-March 2004, following endorsement by the Evans Vaccines (Powderject) board of directors. These quality system objectives are also applicable across the Powderject group.

The Quality System Improvement Program (QSIP) objective for 2003/2004 is to redevelop and introduce robust quality systems for:

- Failure investigations, Corrective and Preventative actions
- Engineering Quality
- Documentation Management and Control
- Validation and Requalification
- Vendor Assurance
- IT Compliance

Each of the systems has been assigned to a site operations manager who reports directly to one of the Liverpool site executive management team members. In addition to one-on-one discussions between the operations manager and their site executive line manager, the site executives also have a defined program to monitor delivery against the objective, whereby the operations manager responsible for the delivery of the objective is required to present updates to the Liverpool site executive management committee in accordance with a defined plan.

We recognize that quality improvement is a continuous process. We continue to review our systems and processes and implement improvements throughout all our operations. The quality system objectives for this year do however recognize that we need to prioritize, so that we have a manageable program of quality system improvements, which will deliver sustainable improvements throughout our business.

In order to further enhance our understanding of the gaps, and improvements required to sustain our quality systems, and furthermore, to benefit from additional expertise in developing our way forward, we have selected the [redacted], to assist us.

[redacted] have specific expertise to enable them to support our quality improvement initiative. Attachment 6.1 (Page 530) contains the Quality System Improvement Plan (QSIP).

The QSIP reflects the desire of Evans Vaccines to improve management control over the quality system, as part of its overall business responsibility and as required by FDA. As such, this initiative was commissioned by Evans Vaccines (Powderject) management committee and features their oversight of the process, review of the findings and support for improving quality systems as may be revealed by this study.

If you should have any questions, please contact Dr. Jim C. Williams, Vice President U.S. Regulatory Affairs and Authorized Official, Liverpool facility at 978-836-7006 / 608-231-3150 or Mr. John O'Brien (Head of Operations, Liverpool facility) at +44 151 705 5083.

Yours sincerely

Mr. A. H. Sneddon
Site Director

Enc. Mrs. Omotunde Osunsanmi, CSO, CDER
Dr. Robert W. Jennings, CSO, CDER
Dr. Robin Levis, Regulatory Coordinator, CBER
Mr. Jonathan McInnis, Biologist, CBER
Dr. J. C. Williams, Vice President U.S. Regulatory Affairs / Authorized Official
Mr. J. O'Brien, Head of Operations, Evans Vaccines Limited.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
1431 Harbor Bay Parkway
Alameda, California 94502
Telephone: (510) 337-6847
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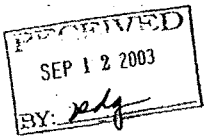
September 3, 2003

Mr. Andy Sneddon
Site Manager
Evans Vaccine, Limited
Gaskill Road Speke
Liverpool L24 9GR, United Kingdom



Dear Mr. Sneddon:

We acknowledge receipt of your letter dated June 27, 2003, which responds to the Form FDA 483 issued at the conclusion of the June 2-10, 2003 FDA/Team Biologics inspection of the Evans Vaccines Limited (Evans), Liverpool, United Kingdom facility. The response will be placed in Evans' permanent file, and corrective actions will be reviewed and assessed during the next inspection.

Sincerely,

Philip R. Lindeman
Compliance Officer
ORA/Office of Enforcement
Division of Compliance
Management Operations

Cole, Elaine

From: Hornatko-Munoz, Adrienne
Sent: Wednesday, August 25, 2004 4:06 PM
To: Cole, Elaine
Subject: FW: information alert draft

Importance: High

At present, I hear a Chiron/OVRR/CDC conference plus Phil Russell is on the line.

-----Original Message-----
From: Meyer, Mary
Sent: Wednesday, August 25, 2004 3:34 PM
To: Hornatko-Munoz, Adrienne
Subject: FW: information alert draft

-----Original Message-----
From: Midthun, Karen
Sent: Wednesday, August 25, 2004 3:30 PM
To: Delman, Dana; Osborne, Walter
Cc: Goodman, Jesse; Elengold, Mark; Maloney, Diane; Egan, William; Baylor, Norman; Weir, Jerry P.; Levandowski, Roland A.; Cohen, James S; Eltermann, John; Meyer, Mary; McNeill, Lorrie
Subject: FW: information alert draft

-----Original Message-----
From: Weir, Jerry P.
Sent: Wednesday, August 25, 2004 2:48 PM
To: Egan, William
Cc: Baylor, Norman; Midthun, Karen; Maloney, Diane; Levandowski, Roland A.
Subject: FW: information alert draft

Dana and Walt,
Office of Vaccines had a conference call with Chiron-Evans earlier today in which Chiron informed us that 8 lots of influenza vaccine have bacterial contamination. They are investigating the cause, and are also retesting all of the other lots of vaccine to ensure that those are negative for contamination. Because of these events, Chiron projects that it will not be able to start releasing vaccine to the market until October at the earliest. Chiron had originally planned on being able to start releasing vaccine this month. So there will definitely be a delay in the availability of the Chiron influenza vaccine, and there will be some decrease in the overall number of doses. The details are in the attached info alert. If you need additional info, please call me (301-827-0372).
Karen

InformationAlertdra
ft08-25-04R...

Information Alert

Date: August 25, 2004

Subject: Significant delay of release of the inactivated influenza virus vaccine produced by Chiron Vaccines for the 2004-2005 influenza season

Why this information is Important for the Secretary Now: The supply of inactivated influenza virus vaccine for the United States will be delayed for the upcoming flu season and, depending on the outcome of on-going studies, this supply may be reduced. Eight (8) lots of influenza vaccine have been found to be contaminated with a Gram-negative bacterium, *Serratia marcessans*; this represents a loss of approximately 4 million doses of vaccine out of a projected 52 million doses of vaccine planned by Chiron for distribution in the United States. Additional sterility testing on all lots of influenza vaccine that have been produced to date by Chiron are being conducted by the company; to date, approximately 50% of the already-produced lots of vaccine have been sterility tested by Chiron and have been shown to be negative; the testing of the remaining lots is on-going, as is an investigation for the probable root-cause of the sterility failures.

Summary of Issues, Background, and Department Response/Actions:

- Chiron Vaccines and Aventis Pasteur are the two U.S.-licensed manufacturers of inactivated influenza vaccines; MedImmune Vaccines is licensed to produce live attenuated influenza vaccine for use in the United States.
- For the 2004-2005 flu season, Chiron planned to produce approximately 52 million doses of vaccine; Aventis planned to produce approximately 50 million; MedImmune planned to produce approximately 1 million doses of vaccine. Manufacturing at all three is still in progress. Based on past years demand and recent ACIP recommendations, it has been estimated that approximately 100 million doses of vaccine will be needed this year for the United States.
- While performing release testing, Chiron discovered that 8 lots of filled, trivalent vaccine manufactured for this year's flu season were contaminated with *Serratia marcessans*, a Gram-negative bacterium.
- The source of the bacterial contamination is still under investigation at Chiron, but testing of vaccine components indicates that the B/Jiangsu/10/2003 monovalent bulk component was contaminated and is the probable root source of contamination for the final 8 lots of the trivalent product.. Chiron suspects a procedural breach in aseptic technique resulted in the introduction of the bacterial organism. The investigation is continuing and has, to date, not revealed other contaminated monovalent or trivalent lots.
- Chiron indicates that it has not and will not release any vaccine for distribution and use until their investigation is completed. Chiron indicates that final release of vaccine will not begin until October at the earliest and not, as originally planned, in August and September, with completion in October.
- Chiron indicates that the 8 contaminated lots represent a loss of approximately 4 million doses of vaccine. Chiron indicates that continued manufacturing can make up a portion of the lost doses, but output is estimated to be at least 2 million doses less than initially planned.

- Chiron indicates that this situation will be discussed later today with the NVPO and CDC. Chiron intends to issue a press release on Friday August 27, 2004 to inform the public of this situation.
- FDA/CBER/OVRR is working closely with Chiron to monitor and resolve the situation.

Contacts:
William Egan, FDA/CBER/OVRR, [redacted]
Jerry Weir, FDA/CBER/OVRR/DVP, [redacted]
Roland Levandowski, FDA/OVRR/DVP, [redacted]

Egan, William

From: Cole, Elaine
Sent: Thursday, September 09, 2004 11:27 AM
To: Meyer, Mary; Cohen, James S; Levandowski, Roland A.; Strickland, Dennis; Malarkey, Mary; Baylor, Norman; Eltermann, John
Cc: Egan, William; Midthun, Karen; Goodman, Jesse; Morrison, Ellen F
Subject: Conference call summary- Chiron 's Fluvirin

This email summarizes a 9/9/2004 conference call among Chiron staff (multiple locations), CDC and CBER (Dr. Egan and I) to update all parties on the status of Chiron's investigation into the non-sterility of certain not-yet-marketed lots of their influenza vaccine.

Chiron is continuing its planned investigations into the non-sterility finding; work is on track and they are confident that they will be able to identify the root cause of the problem in time to have 46-48 million doses available to the US market in early October 2004. Product will not be distributed until all of the data are evaluated. (Testing so far has included in-house lots as well as tests on earlier stages of the production process, with negative test results.)

Chiron has seen only limited media coverage recently; most of that has been articles in local press, rather than national coverage.

Chiron plans to issue a press statement to update the public in the next week or 2 to summarize the progress of their investigation. They will send the statement, or at least the concepts if not the actual document, to FDA and CDC a day or 2 before it issues, so that the federal agencies will be able to respond to inquiries about it.

An MMWR issue goes to print on 9/24 and will contain an update on flu vaccine availability, including the general nature of the upcoming Chiron press statement (lead time issues for the MMWR will likely preclude the actual Chiron statement being in CDC's article.)

Since there have been some rumors in the healthcare/immunization community about possible flu vaccine shortages, FDA and CDC will be in contact with each other to potentially post a short statement to dispel fears of shortages and to state that, overall, more vaccine is expected to be available this season than last year. (OCTMA and OCBQ, please note.)

Chiron reported that the Senate Ageing Committee (chaired by Larry Craig?) may have an exploratory hearing in the near future on the availability of flu vaccine and its impact on the health of senior citizens. This committee held a similar hearing in 2000 or 2001.

(Another status update call will be held in a week.)

Dr Graham
Susan Bond

Briefing note

CHIRON VACCINES, SPEKE, LIVERPOOL: INFLUENZA VACCINE

The Medicines and Healthcare products Regulatory Agency has today suspended Chiron Vaccines manufacturer's licence in respect of influenza vaccine for a period of 3 months with immediate effect. A result of this action is that the company will not be able to release any batches of their influenza vaccine to any market.

The company was due to supply about 20% of the UK requirement for 2004, with the first deliveries due by 13th September. The company was also due to supply influenza vaccine into the [redacted] and the USA during September and October. The company was committed to supplying up to 48 million doses to the USA.

Background information

Chiron Vaccines (formerly Evans Vaccines) whose manufacturing site is based in Speke, Liverpool, informed the MHRA at the end of August 2004 that some batches of influenza vaccine vials destined for the USA had failed sterility tests. The company assured the MHRA that single dose vaccine for the UK market was unaffected because of [redacted]. However, the company reported that all batches of European and USA product had been quarantined pending the findings of an internal investigation into the sterility failures.

An expert inspector from the MHRA's inspectorate, accompanied by another inspector, visited Chiron's manufacturing site on 13th and 14th September on a fact-finding mission. They discovered that the company was first aware of problems relating to microbial contamination in an intermediate monovalent component of the trivalent vaccine in April 2004 and that their investigation had been running since then. Microbial contamination was found subsequently in product and the manufacturing environment. The first sterility test failures occurred in July in stock destined for supply to the USA. The inspectors were informed that the company's draft investigation report would be available on 24th September. Meanwhile no batches of influenza vaccine would be released. A report of the inspectors' visit was heard by the MHRA's Cross-Agency Vaccine Group on 15th September, when it was agreed that a further visit should take place following a review by the MHRA of the company's internal report.

The company's draft report was reviewed in detail on the 24th September by the Acting Director of the MHRA's Inspection and Enforcement Division and the expert inspector who had visited the site the previous week. They concluded that the report had not addressed the root causes of the contamination problems being experienced by the company. A "for-cause" visit to the site by two inspectors was arranged for 28th-30th September and the company was requested, in writing, not to release any batches of influenza vaccine to any market pending that visit.

The inspectors findings from the "for-cause" visit were presented to a meeting of the Cross-Agency Vaccine Group attended also by a representative from DH Infectious Diseases Division, one from DH Immunisation Policy unit and a [redacted] from [redacted] on 1st October. The inspectors listed 19 serious issues relating to microbial contamination and potential for microbial contamination in influenza vaccine production. These constituted a critical situation regarding sterility assurance of the production process, leading to potential and actual microbial contamination of the finished product by a pathogenic organism. The decision of the meeting was that the inspector's report should be referred to the MHRA's Inspection Action Group (IAG) for consideration of adverse licensing action.

The IAG is a non-statutory committee constituted to consider referrals concerning licensing issues and to make recommendations for adverse licensing action to the Licensing Authority, represented by the Director of the MHRA's I&E Division. The Group met on 4th October and recommended that Chiron Vaccines manufacturer's licence should be suspended immediately in respect of influenza vaccine for a period of 3 months. This decision was made as a result of the company's failure to comply with the requirements of good manufacturing practice resulting in a potentially serious risk to patients through the administration of a vaccine that may be contaminated.

The company has the right of appeal against continued suspension of the licence after the initial period of suspension, but the suspension remains in force pending any appeal. The suspension may be lifted at any time if the MHRA is satisfied that appropriate corrective actions have been taken by the company and that the MHRA is satisfied that the improvements will be maintained.

The suspension does not affect other products manufactured at the Chiron site in Speke.

If you wish to obtain more detail on the GMP issues identified, we would be pleased to host a teleconference or videoconference.

Contact: (MHRA) Paul Hargreaves
Technical Manager
Inspection and Enforcement Division
Tel +44 20 7084 2599
Fax +44 20 7084 2638
Mob +44 7747 638 369

John Taylor
Acting Director, Inspection and Enforcement Division,
MHRA

5th October 2004

MHRA
Safeguarding public health

Medicines and Healthcare products Regulatory Agency
Market Towers
1 Nine Elms Lane, London SW8 5NQ
General enquiries
Telephone 020 7084 2000 Fax 020 7084 2353
E-mail info@mhra.gsi.gov.uk
www.mhra.gov.uk
Direct line 020 7084 2215
Direct fax 020 7084 2638
E-mail IAGSecretariat@mhra.gsi.gov.uk

5th October 2004

Mr [redacted]
Chiron Vaccines Ltd
Gaskill Road
Speke
Liverpool
L24 9GR

Dear Mr [redacted]

RE: Medicines Act 1968
Suspension of Manufacturer's Licence (ML18532/01) in relation to Influenza Vaccination Products

I refer to the above manufacturer's licence granted to Chiron Vaccines Ltd, the investigative visits conducted by Mr P Hargreaves and Mr A J Trill on the 13th & 14th September 2004 and by Mr P Hargreaves and Mr I Rees between the 28th to 31st September 2004 at your manufacturing and assembly premises at Gaskill Road, Speke, Liverpool, L24 9GR and the representations made by your company (by email) on the 4th October 2004.

The Licensing Authority are, by this letter, exercising their powers under section 28 of the Medicines Act 1968 ("the Act") to suspend the above licence with immediate effect on the grounds that you have to a material extent contravened the provisions of the licence (see section 28 (4) (c)) by failing to conduct your operations in accordance with the principles and guidelines of Good Manufacturing Practice, (see paragraph 3 of Schedule 2 to the Medicines (Standard Provisions for Licences and Certificates) Regulations 1971 (SI 1971/972)). The suspension is limited to influenza vaccination products.

In view of the serious nature of the deficiencies identified as a consequence of the visits and the potential risk to public health if the products in question were to be released, it appears to the Licensing Authority that in the interests of safety it is necessary to suspend the manufacturer's licence (ML18532/01) in relation to all influenza vaccination products with immediate effect. In accordance with paragraph 11 of Schedule 2 of the Act, the licence is suspended with effect from 10:00a.m. on the 5th October 2004, for a period of three months.

Manufacturing and assembly of any influenza vaccination products at your premises must cease immediately. The manufacture or assembly of medicinal products otherwise than in accordance with a licence is prohibited by section 45 of the Act. Any influenza vaccination products manufactured or assembled at the Gaskill Road site since 2nd March 2004 should be immediately quarantined and not released.

A list of the Inspectorate Findings during the 28th to 31st September 2004 investigative visit is appended at annex 1.

Please address any correspondence to the undersigned.

Yours sincerely

Bernadette Sinclair-Jenkins

Mrs Bernadette Sinclair-Jenkins
A person authorised to sign on behalf of The Secretary of State for Health

Annex I

2004 Fluvirin Manufacturing Campaign - Inspectorate Findings

D P Hargreaves, I Rees
30th September 2004

General findings

1. Bioburden.

1.1 Bioburden levels for the 2004 manufacturing campaign were found to be significantly higher by a number of orders of magnitude compared to 2003 and 2002. These levels had been sustained from March 2004 to-date.

1.2 For example, typical result for 2002 and 2003 were ≤1 cfu/ml with 6 – 8 incidents above ___ u/ml, whereas in 2004 the levels have been 10^3 to 10^7. With approximately 50 incidents to-date.

1.3 Non-conformance reports were only raised in June for bioburden levels in excess of ___ :fu/ml reported over the previous 3 months.

1.4 An investigation team was instigated in late March/early April to determine the cause(s) of the increased bioburden. Several possible sources have been identified but no conclusion have yet been reached.

1.5 The number of instances of Gram negative organism contamination in a critical (sterile filtration) manufacturing room has increased significantly during 2004.

1.6 Organisms found in the bioburden are also found in the environment.

1.7 Organisms found in the bioburden have also been isolated from the sterile filtered monovalent bulk and from finished product (vials).

1.8 Environmental monitoring was increased on 17, 18, 19 and 20th of September, then returned to the previous level.

2. Sterile filtration practices:

2.1 Non-sterile monovalent blend pools (MBP) bulk tanks taken into grade ___ filtration area.

2.2 Non-sterile bulk solution aerosol is vented through ___ filters from the non-sterile side of the filter into the grade ___ room in the ___ grade area. The ___ tubing was not securely attached to the vent valve prior to mid September. The SOP for assembly of filter ___ does not require the fitting of vent filters.

2.3 Operators are not dedicated to Grade ___ and Grade ___ ocation activities.

2.4 The level of bioburden in some cases, was at the limit of or exceeded ___ cfu/ml). ___ MBP were re-filtered as a result of being close to or exceeding the ___ bioburden limit.

2.5 2 previous non-conformance reports on contamination (2002) of MBP recommended reducing the number of aseptic connections that have to be made during filtration. These changes have not been implemented.

3 Scale up of production in 2004.

3.1 Increase in egg inoculation from [redacted] (x [redacted] increase). Interim report indicates that there is an [redacted] in processing time and a need for [redacted] to control bioburden.

3.2 Increase in number of [redacted] machines from [redacted].

3.3 Increase in volume by [redacted] % of [redacted] from [redacted] but maintenance of [redacted] results in increased [redacted]

4 Breaches in tank integrity.

4.1 A trivalent tank was found to be leaking in 2003, the trivalent was transferred to a different tank and was not re-filtered. The finished product failed the sterility test.

4.2 Tank integrity was breached in 2004 when the [redacted] the [redacted] was found to be loose, the bulk was transferred to a new tank without re-filtration.

4.3 Tank integrity was breached in 2004 when an [redacted] filter became detached, the filter was re-attached and the bulk was not re-filtered.

[redacted]
From: Baylor, Norman
Sent: Tuesday, October 05, 2004 8:20 AM
To: Goodman, Jesse; Cohen, James S
Cc: Egan, William; Midthun, Karen
Subject: RE: Hheads up Chiron flu vax poss problem

Importance: High

I just got off the phone with Clement Lewin at Chiron. The UK MHRA has suspended the license for Fluvirin for 3 months for non-compliance with UK GMPs. The MHRA faxed us a letter this morning. I have not seen the letter nor do I know where it was faxed. I have Clem on the line now. I will get back to you shortly.

-----Original Message-----

[redacted]
Sent: Tuesday, October 05, 2004 8:10 AM
To: Cohen, James S; Baylor, Norman
Cc: Egan, William; Midthun, Karen
Subject: Re: Hheads up Chiron flu vax poss problem

Sorry meant to include bill and havew called lkm am on my way in
J

-----Original Message-----

[redacted]
To: Cohen, James S <CohenJ@cber.FDA.gov>; Baylor, Norman <baylor@cber.FDA.gov>
Sent: Tue Oct 05 08:05:52 2004
Subject: Fw: Hheads up Chiron flu vax poss problem

-----Original Message-----

[redacted]
To: Elengold, Mark <ELENGOLD@cber.FDA.gov>
Sent: Tue Oct 05 08:00:14 2004
Subject: Fw: Hheads up Chiron flu vax poss problem

-----Original Message-----

[redacted]
To: FDA Deputy Commissioner <Deputy.Commissioner@FDA.GOV>
CC: Bachorik, Lawrence L <LBACHORI@OC.FDA.GOV>
Sent: Tue Oct 05 07:58:39 2004
Subject: Hheads up Chiron flu vax poss problem

Apparently the UK authorities have taken an adverse action re chirons flu vaccine after an inspection. We do not know anything else yet. This could not only indicate a substantive issue but jeopardize US supply. We have a call w chiron at 845 and will let you know what we are able to find out. Bruse gellin at HHS is aware and in fact called me.

Jesse

FDA

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality HFM-670
1401 Rockville Pike, Suite 200 South
Rockville, MD 20852-1448

Sending To: Tes Gutekn

Fax Number: 827 3843

From: Jay Eltermaw
Telephone: (301) 827-3031 FAX: (301) 827-3536

Date: 10/18/2004

Number of Pages: 5 (excluding cover page).

Remarks: Notes from the series of teleconferences on 10/5 with MHRA and Chiron. Note that pages 4 and 5 appear to be internal discussions

Jay Eltermann
meeting notes w/
MHRA and Chiron
[illegible]

1[illegible]/5/2004

– Flu vaccine – emerg issues vaccine
EMEA revoked license
Chiron license suspended for 3 months

– apparently not reviewed by MHRA
"can't release to any market"

MHRA – EMEA putting report thru now – non-technical –
– suspended – impact the export
= suspended license – suspends export
– investigating problem – Liverpool –
– on site – last week
∴ grounds of lack of sterility assurance – !

– appeal right – but cannot do so before 3 months
– won't be able to release any stock

2

- no announce that
  - Semaba Mauceus -

- started is one of monovalent - with divalent
  → 4 or 5 batches
  → end of August - and - recently
- formulation: - bioburden - 10⁹ org / ml - pre filtration
  - suspended 10 o'clock this morning

! company aware of the problem since April!

note: current vaccine is not suitable for us -
- concern shutting on basis of problem - not taking into consideration the benefit of the vaccine and availability -

- meeting with company tomorrow -

- definitive - will not be any FW vaccine
choose
- temporarily suspend license -

export provision of UK law to be reviewed -

unexpected problem -
  may be considered - valid
  may require add'l conversations

- if unpaid the gov't pikes - may not release the press release
- doesn't count as if there is a drawdown -
- reg agency to reg agency - Sec 338(
- Obtain Board - Head - MHRA
- situation - has been resolved -
- what has changed? - ANS - in draft press release was not definitive root cause.
- MHRA involved a [illegible] hydro provider -
- what about Ebola and hospitals -
- contact the distributor -
- distributing has not been notified - expected until press release is issued -

HRA press release is going out now!

4

Essays - cont

- contaminated in Avg - Cake Avg -
- compare with boosted vs isolated - Avg 25
- " " " "

↳ we were

June 2003

→ 1 Bio = OAI → VAI

downgraded

CHIRON | VACCINES

Gaskill Road
Speke
Liverpool
L24 9GR
United Kingdom
Tel: +44 (0) 151 705 5000 Fax: +44 (0) 151 705 5018

To: Dr Cohen	Company: FDA
Fax Number: 00 1 301 827 3381	
From: Andy Sneddon	Date: 5th October 2004
Fax Number: 0151 705 5084	Number of pages including cover: 9
Subject: MHRA Findings / CV Responses	

Dear Dr Cohen,

Please find attached a copy of the MHRA findings together with Chiron Vaccines responses in relation to the UK facility / Fluvirin 2004 campaign.

Regards

Andy Sneddon
Site Director

Response and Documented Impact Assessment to the 2004 Fluvirin Manufacturing Campaign – Inspectorate Findings by D P Hargreaves and I Rees of the MHRA concluded 30th September 2004

1. **Bioburden**

1.1 **Bioburden levels for the 2004 manufacturing campaign were found to be significantly higher by a number of orders of magnitude compared to 2003 and 2002. These levels had been sustained from March 2004 to-date.**

1.2 **For example, typical result for 2002 and 2003 were <1cfu/ml with 6 – 8 incidents above [redacted] cfu.ml, whereas in 2004 the levels have been 10^5 to 10^7 with approximately 50 incidents to-date.**

Response to 1.1 & 1.2

Prior to each batch being approved for further processing, an assessment is performed by QA, which includes a bioburden review.

Assessment of all batches manufactured during the 2004 campaign has been performed and approved by the quality department prior to further processing.

All processing has been conducted in full accordance with the product licence.

The Sterility Investigation report includes consideration of the potential impact of the elevated Bioburden levels in 2004. The data generated substantiates the Quality review process.

1.3 **Non-conformance reports were only raised in June for bioburden levels in excess of [redacted] fu/ml reported over the previous 3 months.**

Response to 1.3

We recognise that deviation reports were not raised until June 2004 for bioburden samples which were greater than the QC alert limit specification. However formal out-of-specification (OOS) reports were raised and communicated by the Quality Control department to Quality Assurance and Manufacturing Operational areas and formally documented.

The first instance of a bioburden result that breached the QC alert limit was on the 05 March 2004 relating to a batch manufactured on the 01 March 2004 (3 day test).

An OOS was raised, documented and communicated as soon as the alert limit was breached. This procedure was followed whenever the QC alert limit was exceeded.

At the time the OOS reports were issued the version of the procedure current at that time (QASP098) required that all potential OOS results required a formal expanded laboratory investigation (including additional testing) before confirmation of laboratory error could be excluded.

QASP098 was updated in June 04 to clarify the position with regard to OOS results obtained for bioburden samples. The updated procedure specifies that Non-conformance reports (NCR) must be raised for all confirmed laboratory OOS results. On issue of this procedure NCR's were raised in accordance with the revised procedure, including retrospectively those relating to all batches manufactured during the 2004 campaign.

1.4 **An investigation team was instigated in late March / early April to determine the cause(s) of the increased bioburden. Several possible sources have been identified but no conclusions have yet been reached.**

Response to 1.4

A formal investigative team was convened in late March 2004 following the identification, assessment and notification (to the Quality Assurance group) of increased bioburden levels. Prior to the formal team being convened actions were initiated to investigate root cause in early March following notification of the initial OOS.

The formal multi-disciplinary team contained representatives from Production, Quality Assurance, Quality Control and Technical Development. A review of the Fluvirin primary manufacturing process was performed and all potential failure modes relating to the elevated bioburden were identified, with action plans initiated.

Based upon the investigation to date no single factor is the cause of the elevated Bioburden, including the scale-up for 2004 campaign. Comparison of the process at the 2003 scale by processing two batches at [redacted] egg scale did not eliminate the bioburden.

1.5 **The number of instances of Gram negative organism contamination in a critical (sterile filtration) manufacturing room has increased significantly during 2004.**

Response to 1.5

The environmental monitoring programme in place involves the evaluation by the quality department of all environmental data and applicable trends. As part of the

routine review of environmental data from the formulation suite we identified an increased trend of Gram negative organisms isolated during April and May. To ensure that this trend did not lead to an unacceptable level, we fumigated the whole formulation suite at the end of May. This action was successful, as confirmed by ongoing environmental monitoring.

It should be noted that there are no confirmed isolates of *Serratia spp.*, within the Grade – LAF unit where the aseptic connections were made – a key assessment criteria for further batch processing as part of the Quality Assurance process.

1.6 Organisms found in the bioburden are also found in the environment.

Response to 1.6

We recognise that we are bringing non sterile [redacted] into the formulation suite for further processing [redacted], followed by sterile filtration in a [redacted] room. The product is transferred into, and within the suite in enclosed vessels in a controlled manner in accordance with written procedures.

Processing is designed to protect the open parts of the process (aseptic connections), whilst the environmental monitoring programme monitors the impact of the process on the environment.

The environmental data indicates that the impact on the facility is minimised, and that no widespread environmental challenge exists.

1.7 Organisms found in the bioburden have also been isolated from the sterile filtered monovalent bulk and from finished product (vials).

Response to 1.7

A full detailed examination and impact assessment was conducted as part of the Fluvirin Sterility Investigation – as documented in section 7.5 of Sterile Filtration and section 9.2 'Summary report on the assembly of sterile connections'.

All the data we have generated clearly demonstrate that the [redacted] µm filter is effective. Therefore, it can be concluded that the bacterial contamination present in the pre-filtration MBP material would be retained by the [redacted] µm filter.

The report concludes that the contaminated monoblends were caused by faulty aseptic connections.

1.8 Environmental monitoring was increased on 17, 18, 19 and 20th of September, then returned to the previous level

Response to 1.8

Environmental monitoring was increased on 17-20th of September 2004 as part of the sterility investigation to confirm the effectiveness of the routine environmental monitoring regime and generate additional data in support of root cause determination. The knowledge generated from this exercise has been evaluated, and subsequent enhancements to the environmental monitoring programme were developed. The revised regime was presented during the MHRA inspection on 28-30 September 2004. This programme is being implemented.

2. Sterile Filtration Practices

2.1 Non-sterile MBP tanks taken into Grade — filtration area

Response to 2.1

We recognise that we are bringing non sterile bulk into the formulation suite for sterile filtration. The product is transferred into the formulation suite via written cleaning procedures, and handled within the suite in enclosed vessels in a controlled manner in accordance with written procedures.
Processing is designed to protect the open parts of the process (aseptic connections), whilst the environmental monitoring programme monitors the impact of the process on the environment.

2.2 Non-sterile bulk solution aerosol is vented through — filter from the non-sterile side of the filter into the grade — room in the — grade area. The ——— tubing was not securely attached to the vent valve prior to mid-September. The SOP for assembly of filter ——— does not require the fitting of vent filters.

Response to 2.2

The — um filter ——— are vented into the grade — area to ———— ——— filtration. The vent filters are ———————— which ———————————

There is no evidence that aerosols of non-sterile bulk are vented through these filters.

There is no evidence that security of the tubing attachment was an issue. Based on a recommendation from MHRA during a previous inspection (13-14 September 2004) [redacted] were introduced.

Although the SOP did not specifically require the fitting of a vent filter, it was standard practice, and is verified within the manufacturing instruction to perform [redacted] filter integrity test [redacted] the filters connected with the vessel. These filters (including the vent filter) are listed in the MI. The SOP will be updated to clarify the requirement for fitting of the vent filter.

2.3 Operators not dedicated to Grade [redacted] and Grade [redacted] ocation activities.

Response to 2.3

Within the Formulation Department, [redacted]

1. [redacted] of MBP (non-sterile)
2. Sterile Filtration of MBP
3. Blending of Trivalent bulks

The rooms where these operations take place are all Grade [redacted] with localised Grade [redacted] ureas for aseptic connections. Operators were dedicated to specific processes, but not specific tasks within those processes.

On completion of aseptic connections operators perform hand plate monitoring and subsequently change their outer gloves before performing any further activity. Operators perform frequent hand sanitisation with [redacted]

To enhance sterility assurance the dedication of operators to Grade [redacted] nd Grade [redacted] tasks within a specific process (eg sterile filtration) is being reviewed as part of our wider Quality System Improvement Plan (QSIP) .

2.4 Level of bioburden in some cases was at limit/exceeded [redacted] cfu/ml). 12 monovalent blend pools (MBP) were re-filtered as a result of being close to or exceeding the [redacted] bio-burden limit.

Response to 2.4

As the bioburden sample can only be taken immediately prior to filtration, the result is available following completion of the sterile filtration operation. A calculation is then performed. If the bioburden of the pre-filtered monoblend pool

exceeds _ a refiltration is performed, in accordance with the approved SOP.

An NCR is raised each time a monoblend pool is refiltered as shown in the batch records and the NCR logs.

In addition, in house studies carried out using factory isolated *Serratia spp* in Fluvirin, have demonstrated that the µm filter will retain a challenge higher than the manufacturers stated

2.5 **2 previous non-conformance reports for contamination (2002) of MBP recommended reducing the number of aseptic connections that have to be made during filtration. These changes have not been implemented.**

Response to 2.5

In relation to the 2002 non conformance reports, there is no documented evidence of a review of the number of aseptic connections having been carried out, however, discussions with staff involved indicate that a review was performed. Our understanding is that there was no scope for reducing the number of connections at that time.

As part of our continuous quality improvement in manufacturing technologies and GMP we are currently evaluating

Also, as part of the site Quality Systems Improvement Programme (QSIP), a sterility assurance robustness programme has been initiated. A review of aseptic connections is within the scope of this programme.

3. **Scale up of production in 2004**

3.1 **Increase in egg inoculation from % increase) Interim report indicates that there is an in processing time and a need for to control bioburden**

Response to 3.1

A random sample of temperature data points taken across the 2003 and 2004 campaigns has been reviewed to confirm the recorded temperature of the harvested allantoic fluid. Although there is a slight in processing time (approx year on year, the actual temperature of the harvest fluid is no higher in 2004 (C) than in 2003 (C).

This is considered to have no significant impact in terms of process scale-up.

3.2 **Increase in number of [redacted] machines from [redacted].**

Response to 3.2

This increase is in excess of the number of input eggs used within the process.

During the 2003 campaign, when a capacity increase from 2002 took place, additional centrifuges were installed to support the campaign. However these did not become fully operational until mid way through the campaign. The data demonstrates that the bioburden level remained constant throughout irrespective of the number of centrifuges utilised.

3.3 **Increase in volume by [redacted] % of [redacted] from [redacted] but maintenance of [redacted] results in [redacted] of monovalent blend pools**

Response to 3.3

The increased number of [redacted] processed by [redacted] necessitates [redacted]. The procedure requires [redacted]. This [redacted] ratio is consistent across both 2003 and 2004. Nevertheless it is correct that the final [redacted] on completion of the [redacted] process has [redacted]. Due to this, consideration has been given to the impact on sterile filtration parameters. In particular, the pre-filtered monovalent blend pool at [redacted] may lead to a [redacted].

Process parameters have been reviewed and compared to what is considered as worst case for filtration using the [redacted]. Based upon the review, the process parameters used for Fluviria filtration do not approach worst case and it is considered that the scale-up of the process for 2004 has not had a detrimental effect on the filtration of the monovalent blend pools.

In 2004 we have specifically processed two batches at the 2003 scale ([redacted] eggs) the results from which confirm no significant impact on downstream processing due to the scale-up.

4. **Breaches in Tank Integrity**

4.1 **An MBP tank was found to be leaking in 2003, the monovalent was transferred to a different tank and was not re-filtered. The finished product failed the sterility test.**

Response to 4.1

The statement, as discussed during the close out meeting is incorrect, and should read: A **trivalent** tank was found to be leaking in 2003, the **trivalent** was transferred to a different tank and was not re-filtered. The finished product failed the sterility test.

The standard site practice for potential breaches of tank integrity is to assess each case individually. If the result of the assessment is that integrity has not been breached then contents are transferred as a precautionary measure. Environmental monitoring is carried out during the operation and sterility samples are taken before and after the transfer. An NCR is raised each time a tank transfer occurs. This particular incident is documented in NCR 2003/1874/03.

Re-filtration of trivalent product is not part of the validated process.

4.2 **Tank integrity was breached in 2004 when the [redacted] was found to be loose, the bulk was transferred to a new tank without re-filtration.**

Response to 4.2

This particular incident is covered by company NCR procedure. An NCR, which included assessment by Quality Management was completed. The investigation determined that whilst the [redacted] was loose, the actual [redacted] was secure, supported by data from a successful [redacted] test of the tank following product transfer. The data demonstrates that integrity of the tank was maintained.

Re-filtration of trivalent product is not part of the validated process.

4.3 **Tank integrity was breached in 2004 when an [redacted] filter became detached, the filter was re-attached and the bulk was not re-filtered.**

Response to 4.3

This particular incident relates to a trivalent batch and is covered by the company NCR procedure. An NCR, which included assessment by Quality Management was completed. The investigation determined that the integrity of the bulk was not compromised as the [redacted] ubing between the filter and tank was securely clamped.

Re-filtration of trivalent product is not part of the validated process.

Zavagno, Denise

From: Sinclair-Jenkins, Bernadette [Bernadette.Sinclair-Jenkins@mhra.gsi.gov.uk]
Sent: Wednesday, October 06, 2004 10:49 AM
To: Zavagno, Denise
Subject: RE: questions regarding the suspension

Dear Ms Zavagno
I am writing to confirm receipt of your e-mail. I have forwarded your e-mail to the MHRA's legal advisor for consideration.

Bernadette Sinclair-Jenkins
Manager, Divisional Secretariat, Policy and Borderline Unit
Inspection and Enforcement Division
MHRA

-----Original Message-----
From: Zavagno, Denise [mailto:DZavagno@OC.FDA.GOV]
Sent: 06 October 2004 15:34
To: Sinclair-Jenkins, Bernadette
Cc: Raza, Mark
Subject: questions regarding the suspension

> Ms. Sinclair-Jenkins,
>
> Thank you so much for speaking today with Mr. Mark Raza and me regarding
> the suspension of Chiron's license to manufacture flu vaccine. As we
> explained, we are requesting a copy of the law or regulation which
> provides the licensing authority in the United Kingdom with the power to
> order the suspension, so we can better understand how this action affects
> the supply of flu vaccine by Chiron. We also have the following questions
> about the suspension:
>
> 1. Under the law or regulation that led to the suspension, does the
> manufacturer have any remedies once the suspension is ordered? Can the
> manufacturer ask for a hearing, or request that the amount of time
> designated in the suspension letter be shortened? Can the manufacturer
> ask that the batches or lots be retested? Are there any provisions for
> reconditioning the lots?
>
> 2. Could you please explain how the suspension order affects lots that
> were manufactured since March 2? Why was this date chosen? Could you
> please generally describe the evidence to support the fact that lots
> manufactured more than seven months ago are implicated?
>
> 3. What is the status of the lots that have already left the UK and are
> physically located in the USA? Who is in control of those lots and who
> has authority to release them. We understand that a "qualified person"
> must release them, and that the "qualified person" is an employee of the
> manufacturer, but how does he know when and if to release lots? How does
> the authoriy of the MHRA reach these lots once they have left the UK?
>

> Thank you very much for forwarding these questions to your legal
> department. Please do not hesitate to give us a call at the number we
> provided this morning, if you have any questions or comments.
>
>
>
>
>
> Denise M. Zavagno
> Associate Chief Counsel for Biologics
> Food & Drug Division, OGC
> 301-827-1134
> dzavagno@oc.fda.gov
>
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> please e-mail the sender immediately at dzavagno@oc.fda.gov.
>
>
>

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Francer, Jeffrey

From: Zavagno, Denise
Sent: Friday, October 08, 2004 10:57 AM
To: Azar, Alex (OS); Stannard, Paula (OS); Troy, Daniel; Hargan, Eric (OS)
Cc: Raza, Mark; Francer, Jeffrey
Subject: FW: Suspension of Manufacturer's Licence
Importance: High
Sensitivity: Confidential

Alex: I understand you had wanted to review anything forwarded to FDA by Ms. Sinclair-Jenkins in response to the questions I forwarded on Wednesday, October 6. Her response is attached. Please do not hesitate to call me with questions or comments.

Denise Zavagno
Food & Drug Division, OGC
301-827-1134
-----Original Message-----
From: Sinclair-Jenkins, Bernadette [mailto:Bernadette.Sinclair-Jenkins@mhra.gsi.gov.uk]
Sent: Friday, October 08, 2004 9:58 AM
To: dzavagno@oc.fda.gov
Cc: markraza@oc.fda.gov
Subject: RE: Suspension of Manufacturer's Licence
Importance: High
Sensitivity: Confidential

Dear Ms Zavagno

Please find attached a reply to your e-mail of 6 October and an extract of the relevant UK legislation.

Yours sincerely

Bernadette Sinclair-Jenkins
Unit Manager, Policy and Borderline
MHRA

<<Suspension of Manufacturer's Licence.doc>> <<Scanned document.jpg>>

compliance with the Department of Health's policy on the use of electronic communications. For more information on the Department of Health's e-mail policy click here http://www.doh.gov.uk/emaildisclaimer.htm

Friday 8th October 2004

Ms Zavagno
Associate Chief Counsel for Biologics Food & Drug Division, OGC

0207 084 2215
0207 084 2638

Bernadette.sinclair-jenkins@mhra.gsi.gov.uk

Dear Ms Zavagno

Suspension of Manufacturer's Licence

Thank you for your e-mail of 6 October about the suspension of the Chiron Manufacturer's Licence for influenza vaccination products (ML 18532/01).

I will answer your questions in the order in which you raised them:

1. Section 28 of the Medicines Act 1968 (the "Act") provides powers to suspend, revoke or vary a licence under the Act. Schedule 2 to the Act sets out the procedure to be followed by the licensing authority in exercising these powers. Chiron's Manufacturer's Licence was suspended with immediate effect in accordance with paragraph 11 of Schedule 2. There is no appeal mechanism for an immediate suspension. Chiron's licence has been suspended for 3 months.

2. The licence suspension prevents any manufacturing activity from the date specified ie. ~~October 6th~~, October 5th.

The date of March 2 2004 was specified in the suspension letter because that was the date that the company first found high levels of bio burden in the intermediate product ~~m~~monovalent blend pools.

3. I understand that no batches of product were released to market prior to the suspension of the licence. Each batch of product must be certified by a Qualified Person prior to release for sale. For your information I attach a copy of the relevant UK legislation (paragraph 16 of the Medicines (Standard Provisions for Licences and Certificates) Regulations 1971, SI 1971/972). Certification of product is a manufacturing activity, ie. it is an activity carried out under a Manufacturer's Licence. Hence if certification had not taken place before the suspension of the licence, it cannot now take place.

I trust that I have satisfactorily answered your questions.

Yours sincerely

Bernadette Sinclair-Jenkins
Unit Manager, Policy and Borderline
MHRA

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
ORA/OE/DIVISION OF COMPLIANCE MANAGEMENT AND OPERATIONS 5600 FISHERS LANE, ROCKVILLE, MD 20857 USA TEL: (301) 827-0391/FAX: (301) 827-0342	10/10-15/2004 FEI NUMBER

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: ANDY SNEDDON, VICE PRESIDENT OF MANUFACTURING, UK SITE DIRECTOR

FIRM NAME	STREET ADDRESS
EVANS VACCINES an affiliate of CHIRON CORPORATION	GASKILL ROAD
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
LIVERPOOL L24 9GR, UK	VACCINE MANUFACTURER

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DURING AN INSPECTION OF YOUR FIRM (WE) OBSERVED:

1) Regarding Fluvirin Sterility Investigation #R/0198/10/04 dated October 9th 2004:

A) The Fluvirin Sterility Failure Investigation Report states (in part) that [redacted] fumigation took place on May 17, 2004 as a corrective action to increased levels of Gram negative organisms (including *Serratia spp*) during April and May. The area fumigated was the formulation suite. The firm deemed that the fumigation "was successful, as confirmed by ongoing environmental monitoring" and that "it should be noted that there are no confirmed isolates of *Serratia spp.* within the Grade [redacted] LAF unit where aseptic connections are made." The firm further deems this as "a key assessment criteria for further batch processing as part of the Quality Assurance Process". This investigation conclusion is not supported and information reported is inaccurate, in that:

1) the firm does not report that Gram negative rods, oxidase negative, were actually isolated in the formulation areas after the fumigation, further Gram negative rods identified as *Serratia spp.* were also isolated, and

2) there is no evidence that the firm took further action to correct continued excursions of alert and action levels in formulation rooms [redacted] and [redacted] from May 2004 through September 2004. The firm continued to experience alert and action level excursions for Gram negative organisms, including but not limited to, *Serratia spp.*

B) Regarding retest performed on the sterility test failures for four of nine final vial product lots, there is no investigation into the mixed pass and fail sterility test results for the original two lots and two "sister" lots associated with the failed monovalents.

The original two failed lots [redacted] were retested [redacted] times the normal test sample size (normal test sample size is [redacted] vials). The "sister" lots [redacted] of the two original failed lots were also retested [redacted] times the normal test sample size. Results are as follows:

Lot#	Re-Test Date	Results of each set of 40 vials
[redacted]	22 Jul 04	[redacted] set of [redacted] vials passed sterility test sets of [redacted] vials failed sterility test
[redacted]	22 Jul 04	[redacted] sets of [redacted] vials failed sterility test
[redacted]	28 Jul 04	[redacted] sets of [redacted] vials failed sterility test

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
		Omohundo O. Osunsami, CSO Paula A. Trost, CSO John D. Pinkhelwar, Ph.D. Supv. Chemist David S. Cho, Ph.D., Microbiologist Mark A. Elengold,Deputy Director Oper., CBER	15 October 2004

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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TO: ANDY SNEDDON, VICE PRESIDENT OF MANUFACTURING, UK SITE DIRECTOR

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DURING AN INSPECTION OF YOUR FIRM (WE) OBSERVED:
[redacted] 29 Jul 04 [redacted] sets of [redacted] vials passed sterility test
[redacted] sets of [redacted] vials failed sterility test

C) SOP M198, Sterility Investigation Report (Version 06), was not followed during the Fluvirin Sterility Failure investigations in that, the SOP required a Non-Conformance Report (NCR) be initiated in accordance with the NCR SOP. This was not done for the nine filled vial lots that were contaminated with *Serratia spp.* Regarding filled vials, the first failure occurred on 8 July 2004. The 9th failure occurred 2 August 2004. There is no documentation to show that root cause, immediate corrective action, or product impact was addressed at the time of each failure (as per the firm's SOP). One NCR (dated 28 September 2004) was generated to cover all nine sterility failures as well as monovalent blend failures and serves only to refer to the final Fluvirin Sterility Failure Investigation dated 9 October 2004.

D) No documentation of rationale in the Fluvirin Sterility Investigation #R/0198/10/04 dated October 9th 2004 indicating that all three (3) monoblend batches of the Fluvirin trivalent strains with sterility failures are the B/Jiangsu strain.

E) The investigation of the root cause analyses, corrective/preventive actions, conclusions and recommendations did not include B/Jiangsu bulk batch [redacted]. The first of the three (3) monoblend batches implicated in the nine (9) Fluvirin final filled vials sterility failures with bioburden level of 67cfu (specification of [redacted]cfu/ml) but failed sterility at the bulk stage (isolate: *Serratia marcesens).* (Was referenced in the Investigation Report)

F) The investigation did not specifically state that high bioburden levels were noted in the Fluvirin B/Jiangsu strain at the [redacted]/Pre filtration step in [redacted](83%) of [redacted] monoblend batches manufactured for year 2004 campaign with 170-39,000,000cfu/ml bioburden levels per batch (alert level [redacted]cfu/ml). This is higher bioburden than noted for any of the other two Fluvirin monoblend strains.

G) No documentation in the investigation report of the effect of keeping the monoblend/trivalent formulations at [redacted] for up to [redacted] during processing was considered. Fluvirin finished vials are labeled for shipment at 2-8°C and Fluvirin monoblend/trivalent bulks are stored at temperature of [redacted]°C.

H) There is a lack of scientific data to support the statistical rationale for the retest sampling and testing plan.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED
		Omotunde O. Osunkoya, CSO Paula A. Trost, CSO John D. Finkelstein, Ph.D. Supv. Chemist David B. Cho, Ph.D., Microbiologist Mark A. Elengold, Deputy Director, CBER	15 October 2004

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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TO: ANDY SNEDDON, VICE PRESIDENT OF MANUFACTURING, UK SITE DIRECTOR

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EVANS VACCINES an affiliate of CHIRON CORPORATION	GASKILL ROAD
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2) Regarding clean room design and operations for Formulation Room [redacted] (Filtration) and Formulation Room [redacted] (Trivalent Blending): The Class [redacted] (Class [redacted] area where post filtration aseptic connections take place is equipped with [redacted] curtains in the form of strips approximately [redacted] inches wide and are arranged so as to overlap each other and are attached at the ceiling surrounding the HEPA filter. The curtains separate the Class [redacted] area from the Class [redacted] (Class [redacted] area.

A) The curtains are approximately [redacted] from the floor some of the [redacted] strips are bent leaving gaps between each strip. There is lack of assurance that airflow would not be disrupted. Available smoke videos do not provide assurance that there is no disruption.

B) The room is arranged so that operators are required to reach into curtains or beneath the curtains and vigorously manipulate equipment only 6 to 12 inches inside the curtains. During a mock demonstration of operations, one operator was observed making aseptic connections approximately [redacted] from the floor which is [redacted] below the bottom of the curtains and was required by the design of the equipment to disrupt the curtains that separate the Class [redacted] and Class [redacted] areas.

C) The equipment configuration within the Class [redacted] environment is such that operators must crouch in the airflow stream sweeping towards the critical area where multiple aseptic connections are made

D) Available smoke studies do not demonstrate the ability to maintain integrity of laminar airflow within the critical area when operator is present. Furthermore, the operator moves from a Class [redacted] environment into the Class [redacted] environment on multiple occasions during aseptic operations

3) Filtration occurs in Formulation Room [redacted] and trivalent blending occurs in Formulation Room [redacted] Activities involve operators making aseptic connections at pre and post filtration sites. These operations routinely encompass between [redacted] in which operators are performing critical operations. Regarding air environmental monitoring in virus formulation areas, there is a lack of assurance that microbial contamination during critical operations would be adequately detected in that:

A) The firm does not routinely monitor active air while critical operations are taking place. Viable active air sampling is tested using a [redacted] L sample which takes between [redacted] for [redacted] of growth media (a total of [redacted] air sampling).

B) Viable active air sampling that is performed in the Class [redacted] area is not performed in the area where most critical operations are occurring but rather, the air sampler is placed on tables [redacted] different locations at [redacted] different times) near the corners of the Class [redacted] area.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
		Omotunde O. Osanyenwo, CSO Paula A. Trost, CSO John D. Fishbohner, Ph.D. Supv. Chemist David S. Cho, Ph.D., Microbiologist Mark A. Elengold,Deputy Director Oper., CBER	15 October 2004

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
TO: ANDY SNEDDON, VICE PRESIDENT OF MANUFACTURING, UK SITE DIRECTOR

FIRM NAME	STREET ADDRESS
EVANS VACCINES an affiliate of CHIRON CORPORATION	GASKILL ROAD
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
LIVERPOOL L24 9GR, UK	VACCINE MANUFACTURER

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C) Settling plates are not placed in areas where the most activity is occurring and not in areas of critical operations.

D) There is a lack of assurance that the current sampling volume for non viable particulate of [redacted] cu ft/[redacted] is adequate in relation to the time required to perform operations [redacted]. Sampling is not routinely performed in the area of critical process at the time of critical process.

4) Regarding Control of Bioburden in the Manufacturing Facility:

A) [redacted] (60%) out of [redacted] Fluvirin monoblend batches used in the formulations of the trivalent batches manufactured for year 2004 Fluvirin Campaign were out of bioburden alert level of [redacted]cfu/ml with bioburden levels as high as 39,000,000cfu/ml.

B) Out of Specification (OOS) batches of Fluvirin monoblends: A/Wyoming, B/Jiangsu and A/New Caledonia were noted as a result of the high bioburden levels in Observation 2A above and total of 26 out of [redacted] monoblend batches resulted in OOS results for endotoxin levels of up to 5052 Eu/ml (alert level specification for US [redacted] Eu/ml). The monoblends with high endotoxin levels were not used for USA Fluvirin market.

C) Approximately 80% of all microorganisms' growth in the Fluvirin filling room, monoblend aseptic filtration, and trivalent formulation room excursions were not identified to the genus level.

D) Per Non-conformance Report #2004/1071/07 dated July 5th, 2004 Mycoplasma growths were confirmed for Fluvirin A/Wyoming Master Seed batch [redacted] and Working Seed batch [redacted]. Also, per M/2004/1029 dated March 15th 2004, Mycoplasma growth was also confirmed on A/Wyoming Working Seed batch [redacted]. The contaminated seed lots were used in five Fluvirin monoblend batches that were later rejected.

E) Bioburden investigation is incomplete in that there is a lack of documentation that water quality was directly investigated as a potential for contribution to bioburden though purified water does have direct contact with the egg product mixture. For example, purified water is used to clean equipment, including the [redacted] Centrifuge, the [redacted] Centrifuge and [redacted] Machine which come into direct contact with product.

F) Besides the nine (9) batches of Fluvirin that were rejected for sterility failures (Investigation # R/0198/10/04 dated October 9th 2004), additional four (4) batches of finished Fluvirin vials were also rejected due to environmental excursions. For example:

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
		Omolade O. Owoseni, CSO Paula A. Trost, CSO John D. Finkbeiner, Ph.D. Supv. Chemist David S. Cho, Ph.D., Microbiologist Mark A. Elengold, Deputy Director Oper., CBER	15 October 2004

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: ANDY SNEDDON, VICE PRESIDENT OF MANUFACTURING, UK SITE DIRECTOR

FIRM NAME	STREET ADDRESS
EVANS VACCINES an affiliate of CHIRON CORPORATION	GASKILL ROAD
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
LIVERPOOL L24 9GR, UK	VACCINE MANUFACTURER

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DURING AN INSPECTION OF YOUR FIRM (WE) OBSERVED:

1) Per Non-Conformance Report #2004/1632 dated September 9th, 2004 lot [redacted] was rejected due to growth of *Micrococcus spp* on Fluvirin filling needle swab. In addition, two alert levels with microbial growths identified as Gram positive cocci/Gram negative rods were also identified in the [redacted] change room" and within the grade [redacted] area outside of the filling room sterile corridor respectively.

2) Per Non-Conformance Report #2004/1852 dated October 2nd 2004, batch [redacted] *Staphylococcus spp* growth was identified on Fluvirin filling needle swab and on hand plate sample of one aseptic filling room operator. Also alert level growth of *Staphylococcus aureus/Moraxella spp* was detected in the [redacted] change room".

3) Per Non-Conformance Report #2004/1863 dated October 4th 2004, batch [redacted] microbial growth of gram positive cocci were noted in the grade [redacted] aseptic filling room (Class [redacted] Micrococcus spp were noted on hand plate of one operator. Gram negative rod oxidase negative and gram positive cocci/rods were also isolated from setting plates in the changing room.

4) Per Non-Conformance Report #2004/1625 dated September 8th, 2004 batch [redacted] microbial action limits were reached by two (2) Fluvirin filling Operators working in the grade [redacted] aseptic filling area (Class [redacted] In addition, growth of *Brevibacillus brevis, Bacillus subtilis, Micrococcus spp* and Gram negative rods were noted at vial in-feed on the [redacted] filling machine.

G) Although individual investigations were conducted into the following Fluvirin aseptic filling room excursions, no formal overall investigation was conducted to assure adequate corrective and preventive actions.

5) Failure to adequately address root causes during failure investigations, noted during the inspection of year 2003 has not been adequately corrected. For example the previous inspection observation noted:

A) The most recent sterility failure Investigation #R/0198/10/04 for nine (9) filled vials of finished Fluvirin batches concluded that inadequate aseptic technique during aseptic connections was the cause. During the 2003 inspection, the firm was cited for failure to evaluate the reduction in aseptic connection to reduce the possibility of contamination. There is no documentation that adequate corrective action has been conducted.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
		Omotunde O. Onanuga, CSO Paula A. Trost, CSO John D. Finkbeiner, Ph.D. Supv. Chemist David S. Cho, Ph.D., Microbiologist Mark A. Elengold, Deputy Director Oper., CBER	15 October 2004

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
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TO: ANDY SNEDDON, VICE PRESIDENT OF MANUFACTURING, UK SITE DIRECTOR

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EVANS VACCINES an affiliate of CHIRON CORPORATION	GASKILL ROAD
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
LIVERPOOL L24 9GR, UK	VACCINE MANUFACTURER

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DURING AN INSPECTION OF YOUR FIRM (WE) OBSERVED:

B) Control and failure investigations into bulk Fluvirin monoblend/lots at the [redacted] step with high bioburden levels is deficient, in that lots were noted with total high bioburden volumes of $9.66x10^6$ cfu, $7.07x10^7$ cfu & $1.26x10^7$ cfu in year 2000/2001 and 2001/2002 campaigns and no "effect" investigations has been opened to find the root causes of the high levels of bioburden in these lots. **(Not corrected from previous inspection of 2003 in that similar occurrences noted during this inspection)**

6) Regarding Aseptic Media Fills Simulation:

A) Media fill simulations are not representative of actual aseptic fill processes in that, interventions that occurred during aseptic filling processes are not evaluated and considered for incorporation into the media fill simulations. **(Not corrected from previous inspection of 2003)** For example;

Media fills conducted as part of the sterility failure investigation Report #R/0198/10/04 into nine (9) filled vials of Fluvirin batches and routine aseptic media fill simulations per protocol #PQR/0142/04 &PQP/0146/02 failed to include the review and evaluation of batch records for syringes and vials for unusual interventions that occurred during routine aseptic filling processes for incorporation into aseptic fill simulations per: SOP #SCP029 dated October 26th 2003 titled: General Procedure for Routine Monitoring of Aseptic Manufacturing Processes by Process Simulations Utilizing Sterile Media Fills.

B) Deficiencies were noted in the routine aseptic media fill simulations for Fluvirin monoblend aseptic fill /trivalent aseptic formulation simulations, and trivalent media fill simulation investigation into Fluvirin nine (9) filled vials sterility investigation #R/0198/10/04. Aseptic simulations were not representative of actual aseptic fill conditions: Specifically:

1) No Batch record reviews of previously manufactured lots were conducted

2) No documentation that interventions were conducted during the media fills

3) The routine aseptic media fills for the monoblend and trivalent stages do not encompass all interventions normally performed during production.

4) No documentation that worst case challenges were conducted during the aseptic media fills simulations.

7) Regarding quality operations:

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
		Omotunde O. Osunsanmi, CSO Paula A. Trost, CSO John D. Finkbohner, Ph.D. Supv. Chemist David S. Cho, Ph.D., Microbiologist Mark A. Elsegold, Deputy Director Oper., CBER	15 October 2004

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
ORA/OE/DIVISION OF COMPLIANCE MANAGEMENT AND OPERATIONS 5600 FISHERS LANE, ROCKVILLE, MD 20857 USA TEL: (301) 827-0391/FAX: (301) 827-0342	10/10-15/2004
	FEI NUMBER

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: ANDY SNEDDON, VICE PRESIDENT OF MANUFACTURING, UK SITE DIRECTOR

FIRM NAME	STREET ADDRESS
EVANS VACCINES an affiliate of CHIRON CORPORATION	GASKILL ROAD
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
LIVERPOOL L24 9GR, UK	VACCINE MANUFACTURER

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A) Monovalent blend pools produced during the 2004 production campaign that have exceeded the alert limit have been forward processed to final product on multiple occasions, even when bioburden results have exceeded alert limit by multiple orders of magnitude. For process stream excursions of the alert limit that have occurred in the downstream processing steps where purification of desirable components may be completed, it is not clear that the investigation assessed potential product quality impact in terms of microbial metabolites, microbial degradation of the desired vaccine components, or introduction of sensitizing agents into the product.

B) In twenty-four (24) incidences during the 2004 Fluvirin campaign, cultures were used in egg inoculation that exceeded bioburden levels, i.e., [redacted]cfu (alert of [redacted]cfu [redacted]ml). This resulted in the inoculation of approximately [redacted] eggs per batch which were used in the manufacturing of Fluvirin Vaccine with high bioburden containing cultures. Although the firm was aware that the live virus inoculum contained high bioburden, the eggs/batches were not rejected but allowed to continue through the Fluvirin manufacturing process.

C) Technical Report Reference Number R/0123/06/04, revision one, accepted August 12, 2004, states on page 24, "During 2003, no adverse events investigations were performed due to 5 occurrences from one batch." This indicates that no independent review of adverse event reports by batch was performed as a quality control procedure.

8) Regarding zonal centrifugation operations:

A) There is no written procedure or cleaning validation for the manual cleaning of the upper and lower assemblies, which are part of the flow path for the process stream.

B) The written procedure for cleaning of the main body of the zonal centrifuge rotor describes the flushing of process stream contact parts for a period of [redacted] There are no directions describing the surfaces to be flushed.

C) Validation studies for the zonal centrifugation operations characterize material based on [redacted] assays but do not characterize egg proteins, or other specific process or product related impurities.

9) Regarding [redacted] processing tanks utilized in the [redacted] production area where purification operations, sterile filtration, and aseptic formulation operations are conducted:

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		Omobande O. Osunsanmi, CBO Paula A. Trost, CBO John D. Pinkbohner, Ph.D. Supv. Chemist David S. Cho, Ph.D., Microbiologist Mark A. Elsangold, Deputy Director Oper., CBER	15 October 2004

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
ORA/OE/DIVISION OF COMPLIANCE MANAGEMENT AND OPERATIONS 5600 FISHERS LANE, ROCKVILLE, MD 20857 USA TEL: (301) 827-0391/FAX: (301) 827-0342	10/10-15/2004 FEI NUMBER

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: ANDY SNEDDON, VICE PRESIDENT OF MANUFACTURING, UK SITE DIRECTOR

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A) Prior to August 2004, there was no periodic preventative maintenance program or written assessment of aspects potentially effecting tank integrity such as damage to sealing surfaces, sealing gaskets, valve assemblies, or sterile vent filter assemblies. Difficulties with [redacted] valves and integrity of sterile vent filters have been noted in processing.

B) Tanks are usually double door passed through the autoclave into the Class [redacted] formulation areas; however, on some occasions, the vessels have been single door passed back into the vessel preparation area [redacted] and transferred via materials airlock and wiped down into the clean zone.

C) Documentation of sprayball coverage for processing tanks is not found in cleaning validation studies or I/OQ studies for these processing tanks. In addition, the written documentation for visual determination of cleanliness is non-specific relative to assessment of soiling on most difficult to clean surfaces.

D) Cleaning validation for the CIP process for Vessel [redacted] which is utilized in the aseptic formulation of trivalent bulk influenza vaccine, did not include an assessment of sprayball coverage for the vessel. In addition, the study did not include swab sampling of the transfer lines used in the transfer of monovalent blend pools into the mixing vessel [redacted], and for transferring the aseptic trivalent formulated bulk back into a sterilized [redacted] liter tank in formulation room [redacted]

10) Manufacturing instructions (batch production record) do not always capture important processing information. For example, processing tanks are not traceable within the batch production record. In addition, it is not possible to consistently trace processing tanks to specific unit operations for a specific lot.

11) The specified replacement schedule (annual replacement) for the [redacted] filtration [redacted] is not supported by production history accumulated since January 2003. For example, [redacted] sets of [redacted] have been used in the 2003 production campaign, and [redacted] in the 2004 campaign. The stated reason for change after initial annual installation is fouling of the [redacted] resulting in longer processing times.

12) Regarding equipment supporting manufacturing operations in the Egg Virus Unit (EVU):

A) There is no spray ball coverage cleaning studies for the harvest tank, bulk holding tank, inactivation vessel [redacted], and inactivation vessel [redacted]

B) There are no studies to determine the swab sampling sites for the harvest tank, bulk holding tank, inactivation vessel [redacted] and inactivation vessel [redacted]

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		Omolunde O. Osunsami, CSO Paula A. Trost, CSO John D. Finkbeiner, Ph.D. Supv. Chemist David S. Cho, Ph.D., Microbiologist Mark A. Elengold, Deputy Director Oper., CBER	15 October 2004

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
ORA/OE/DIVISION OF COMPLIANCE MANAGEMENT AND OPERATIONS 5600 FISHERS LANE, ROCKVILLE, MD 20857 USA TEL: (301) 827-0391/FAX: (301) 827-0342	10/10-15/2004 FEI NUMBER

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TO: ANDY SNEDDON, VICE PRESIDENT OF MANUFACTURING, UK SITE DIRECTOR

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13) There is no documentation that a manufacturing quality review was conducted in a timely manner on adverse event reports received for twenty-two batches of Fluvirin manufactured in the 2003/2004 campaign where one or more criteria for manufacturing investigation were met per SOP MPD-0022 (Section 7.7), SOP MPD-024 (Section 7.5), and (Section seventeen page 41) of the June 27, 2003 response to the June 10 FD483).

For example:

A) Seven adverse event reports received for injection site type reactions to batch number 765484

B) Ten adverse event reports received for injection site type reactions to batch number 765751

C) Five adverse event reports received for injection site type reactions to batch number 766053

(Incomplete corrective action to the previous inspection of 2003)

14) Regarding product equipment compatibility study:

The [redacted] Tubing used throughout the Fluvirin manufacturing process to transfer centrifuged, formulated and finished product for filling was out specification of [redacted]mg for USP Non-Volatile Residue with result of 1327mg per [redacted] test result. No investigation, corrective and preventive action has been conducted and no justification/rationale is provided for the lack of investigation. **(Incomplete corrective action from previous inspection of 2003)**

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
		Oseloka O. Onyewuenyi, CSO Paula A. Trost, CSO John D. Finkbeiner, Ph.D. Supv. Chemist David G. Cho, Ph.D., Microbiologist Mark A. Stengard, Deputy Director Oper., CBER	15 October 2004

FORM FDA 483 (4/03) PREVIOUS EDITION OBSOLETE (PSC Media Arts (301) 443-1090 EF) INSPECTIONAL OBSERVATIONS PAGE 9 of 9 PAGES

The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under unsanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."

M 3154

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

OCT 21 1999

CBER-99-002

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. John E. O'Brian
Head of Primary Production
Medeva Pharma Ltd
Gaskill Road, Speke
Liverpool, United Kingdom L24 9GR

Dear Mr. O'Brian:

The Food and Drug Administration (FDA) conducted an inspection of your facility located at Gaskill Road, Speke, Liverpool, UK, between July 13 and July 21, 1999. During the inspection, our inspectors documented significant deviations from the applicable standards and requirements of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and Title 21 Code of Federal Regulations (21 CFR), Parts 211 and 600-680 as follows:

1. Failure to establish and follow control procedures to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product [21 CFR 211.110(a)] in that:

   a. Fluvirin™ post ultra filtration ([redacted] monovalent pool samples (e.g., batch numbers 751140, 751201, 751288, 751293, 751485, and 751707) exceeded the bioburden internal specification of < [redacted] colony forming unit (cfu)/milliliter (ml) with bioburden levels ranging from [redacted] cfu/ml to [redacted] cfu/ml. These monovalent pools were refiltered and used to formulate influenza virus vaccine.

   b. The sterile filtration and blending processing steps of Fluvirin™ monovalent pool and trivalent bulk have not been qualified since 1993 and 1992 respectively.

c. The processing hold times for pooled zonal concentrate and split antigen concentrate have not been validated.

d. Fluvirin™ reprocessing standard operating procedure (SOP BLE024) does not include the number of times a reprocessing step can be repeated and a time limit for re-filtration of monovalent pool with high bioburden results.

e. Stability data is not available to demonstrate that refiltered monovalent blend does not affect the stability of the final drug product (Fluvirin™.)

2. Failure to ensure that reprocessed batches will conform with all established standards, specifications, and characteristics [21 CFR 211.115(a)] in that any monovalent blend pool with unacceptable endotoxin level may be reprocessed by [redacted] and concentration in the [redacted] ultrafiltration system; however, there is no data available to demonstrate that this system has been validated to remove unacceptable levels of endotoxin.

3. Failure to establish a written testing program designed to assess the stability characteristics of drug products [21 CFR 211.166(a)] in that there is no data available to demonstrate that through the influenza virus vaccine shelf life the thimerosal concentration is adequate to control bacteria and fungi and the vaccine is sterile since preservative content and sterility testing are not done at expiry.

4. Failure to clean, maintain, and sanitize equipment and utensils at appropriate intervals to prevent malfunction or contamination that would alter the safety, identity, strength, quality, or purity of the drug product [21 CFR 211.67(a)] in that cleaning validation studies of all product contact equipment such as the [redacted] ultra filtration unit have not been completed.

5. Failure to establish and follow appropriate written procedures designed to prevent microbial contamination of drug products purporting to be sterile and to assure that such procedures include validation of any sterilization processes [21 CFR 211.113(b)] in that:

a. The clean steam system servicing the manufacturing areas after the inactivation stage has not been monitored for conductivity, TOC, and endotoxins since November 1998.

b. There is no documentation that during the aseptic media fills done to the syringe and vial filling units all planned interventions that occur during routine production activities were simulated.

6. Failure to establish separate or defined areas or other control systems for manufacturing and processing operations to prevent contamination or mixups [21 CFR 211.42(c)] in that data is not available to demonstrate that adequate pressure differential is maintained

during filling operations since pressure is monitored [redacted]

We acknowledge receipt of your response dated September 1, 1999, to the Form FDA 483 issued at the close of the inspection. Corrective actions addressed in your letter may be referenced in your response to this letter, as appropriate. Our evaluation of your response follows, and is numbered to correspond to the items listed on the Form FDA 483:

1. Please provide data to support the further processing of intermediates (monovalent blend pool and split antigen concentrate) that exceeded the bioburden and endotoxin internal specifications. In lieu of the final investigation report into the bioburden levels in the process fluid stage of the Influenza Virus Vaccine manufacture, please submit a detailed summary of the conclusions upon completion of the investigation.

   Please provide the rationale for increasing your internal specifications when your investigation as to the cause of elevated bioburden and endotoxin levels has not been completed.

2. Please provide a list of all the critical process steps and the specific test methods used to evaluate those critical process steps during the process validation study for the Influenza Virus Vaccine. Also, please be advised that in the absence of data to support holding times for intermediate products, minimal hold times should be in place until the process validation has been completed.

3b. Although your investigation regarding the cause of elevated bioburden and endotoxin levels has not been completed, you amended your procedure to define the endotoxin and bioburden levels requiring reprocessing. Please provide data to support the selection of these reprocessing levels. Also, please be advised that it is unacceptable to mix monovalent blend pools that exceeded the endotoxin internal specification with monovalent blend pool that met internal endotoxin specification.

   The proposed bioburden limit of [redacted] cfu prior to sterile filtration, as stated in your written procedure BLE024, is unacceptable. The bioburden limit prior to sterile filtration should be based on historical data rather than the bacterial retention capabilities of the sterilizing filter. Please adjust your bioburden limit accordingly.

3d. Please adjust the limit requiring microbial speciation prior to sterile filtration of monovalent blend pool to reflect the new microbial limit selected at this stage of manufacturing.

4. Please provide a summary of the approximately 24 deviation reports that you were not able to locate during the inspection including the type of deviation, at what stage of the process the deviation occurred, and any corrective action(s) implemented.

11. Regarding the two Media Simulation Tests (P0P042 and P0P074):

    a. Please clarify whether a single media fill is defined as a total of [redacted] units filled per [redacted] interventions or [redacted] units filled per intervention.

    b. The media fill protocols do not include the allowable number of contaminants per designated number of filled units.

    c. The protocols do not include the set-up procedures or reference all the steps necessary for media fills as indicated in the aseptic filling validation procedure.

    Regarding the Syringe Filling Line Process Simulation Test (P0P042), the protocol steps for gloves replacements do not always correlate with the instructions and documentation of glove replacements on the recording worksheets.

    Regarding the [redacted] Filling Line Process Simulation Test (P0P074), the protocol does not reference the fill size or the frequency of all interventions such as the addition of stoppers and caps during the fill.

15. Please be advised that the proposed routine monitoring frequency of the clean steam system should be based on historical data.

16. Please be advised that the proposed routine monitoring frequency of the compressed air system should be based on historical data.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deviations. It is your responsibility to ensure that your facility is in compliance with the provisions of the Federal Food, Drug, and Cosmetic Act and all applicable regulations.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions include license suspension and/or revocation. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts.

You should notify this office in writing, within 15 working days of receipt of this letter, of any additional specific steps you have taken to correct the noted deviations and to prevent their recurrence. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your reply should be sent to the following address: U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville pike, Suite 200N, Rockville, MD 20852-1448.

Sincerely,

Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and
Research

Mr. WAXMAN. The Chiron plant in Liverpool was not an ordinary FDA-regulated facility. It is a facility with a history of contamination problems that makes half the supply of the U.S. flu vaccine. The plant should have received the highest priority from the Food and Drug Administration.

Yet the agency ignored glaring problems at the facility and missed repeated opportunities to correct them.

Mr. Chairman, you said you don't want us to point fingers and look at the past, let us look at the future. You even, I thought, said you don't want partisanship invoked in our hearings. I don't know what is partisan about criticizing what has led to, in my view, the situation we are facing today. If you don't learn from the past, you are not going to correct these problems for the future.

I have been in Congress for 30 years. Throughout this period, oversight of FDA has been one of my highest priorities. I drafted many of the major laws that the agency implements, including the Orphan Drug Act, the Hatch-Waxman Act, the Nutrition Labeling and Education Act, the Safe Medical Devices Act, the user-fee law that accelerated drug approvals, and the Food Quality Protection Act. That is why I have become so concerned about how the agency has performed in recent years.

What we are witnessing is the dismantling of FDA's enforcement and oversight capabilities. In area after area, the agency is failing to enforce the public health laws that Congress enacted. Enforcement actions for misleading drug advertisements have dropped 70 percent since 2001. Enforcement actions at vaccine plants and other manufacturers of biologic drugs have dropped over 80 percent. Key food labeling laws are being ignored.

And there is no better example of what is wrong at the FDA than its failures at the Chiron vaccine facility.

The story told in the FDA documents begin in June 2003, when a team of FDA inspectors visited the Liverpool facility and found 20 serious problems at the plant, including bacterial contamination and poor sanitary practices. The FDA experts who conducted the inspection recommended the agency take official enforcement action against the company. Yet this recommendation was rejected. FDA downgraded its response and asked the company to make only voluntary reforms.

FDA's justification for failing to cite the facility is that the agency thought conditions were improving. But conditions weren't improving, they were deteriorating. Over the next 16 months, as production at the facility increased, the problems found in June 2003 mushroomed. Yet during this entire period, the FDA never once revisited the plant to see if Chiron was correcting its problems and making safe vaccines. Incredibly, FDA remained passive even after October 25, 2004, when Chiron disclosed that millions of doses of vaccine were contaminated by a potentially lethal form of bacteria.

A responsible regulator would have inspected the plant, demanded to review its production records, and convened high-level meetings of the agency's top experts. That is exactly what the British regulators did. A senior British health official summed up their philosophy as "seeing is believing."

By contrast, FDA conducted oversight by conference call, trusting a stream of false assurances by Chiron that the plant had no seri-

ous problems. FDA conducted no inspection; it reviewed no plant records; and it was caught completely by surprise when British regulators shut down the plant on October 5.

FDA's laxity has had a heavy cost. If FDA had ensured that the problems identified in June 2003 were fixed, this year's flu crisis might never have happened. And if FDA had responded aggressively to the contamination problems in August, our public health system would have had critical extra weeks to prepare for the shortage and to avoid the chaos that ensued in October.

It is essential for FDA to learn from its mistakes. But, so far, the administration has been unwilling even to admit them. In recent weeks, the President, the HHS Secretary, the Acting FDA Commissioner have all reassured the public that FDA did everything right. The Acting Commissioner has even indicated he would do it all over again, the same way.

And I might point out that all those assurances, given all before the election, might be viewed as partisan, because there at least we were facing election. We don't have an election now; the election is over. So if we are critical of something that is going on through oversight, that shouldn't be attacked as partisan.

After the flu crisis broke, Dr. Crawford told the public that the June 2003 inspection had "no relevancy" to the problems found in 2004. He said that FDA monitored the actions of Chiron and assured that the violations found in 2003 were corrected. And he said that the United States and British regulators had acted "in synchrony."

Well, none of these statements are true. In this administration, inconvenient facts are simply ignored. This is a dangerous way to govern and is particularly hazardous for the public health.

I expect the chairman may disagree with me today about the interpretation of some of the FDA documents. That is his right. But even as we disagree over specifics, I want to commend the chairman for his approach to this hearing. He has asked for the right documents, he has worked with us to ensure that we can release redacted copies so that Members and the public can judge their significance for themselves. That is exactly the right way to approach this important hearing. And I hope, after we have had a chance to hear the testimony and ask the tough questions, that we will feel better informed about what happened to make sure that it doesn't happen again.

Thank you, Mr. Chairman.

[The prepared statement of Hon. Henry A. Waxman follows:]

Opening Statement of
Rep. Henry A. Waxman, Ranking Minority Member
Committee on Government Reform Hearing on
Hearing on
"The Nation's Flu Shot Shortage:
Where Are We Today and How Prepared Are We for Tomorrow?"

November 17, 2004

Thank you, Chairman Davis, for holding this hearing on the flu vaccine shortage. You and I share the goal of establishing a healthy vaccine supply in the United States, and effective government oversight is an important part of this process.

This year's flu vaccine crisis raises three important oversight questions.

The first question is how the United States came to depend on just two companies for flu vaccines. The Institute of Medicine, the Government Accountability Office, and the National Vaccine Advisory Committee have all issued reports exposing the weakness of our national vaccine infrastructure. We cannot afford to continue to ignore their recommendations.

The second question is why the vaccine shortage led to such confusion and chaos. In a series of reports over the last four years, GAO repeatedly warned that the United States does not have a plan to ensure that the highest-risk people are immunized in the event of a shortage.

The seniors who have been standing in lines for hours trying to get a flu vaccine know that GAO was right.

The third question is the primary subject of today's hearing: Did FDA do its job to protect the U.S. vaccine supply?

Since the vaccine shortage began, senior Administration officials, including Acting FDA Commissioner Lester Crawford, have been reassuring the public that FDA made no mistakes and did everything possible to protect the vaccine supply.

Today, we will evaluate these claims.

On October 13, Chairman Davis and I asked FDA to provide copies of documents relating to its oversight of the Chiron vaccine plant in Liverpool, England. This is the plant that British regulators shut down on October 5, causing the United States to lose approximately half of its supply of flu vaccine.

We have now received and reviewed over 1,000 pages of documents. We've also met with FDA officials and the Chairman, traveled to England with majority and minority staff to interview British and Chiron officials.

The documents show that FDA failed to provide effective oversight. Expert scientists at FDA knew about serious problems at the Liverpool facility in June 2003, but there was not sufficient leadership at the agency to ensure that they were fixed.

My staff prepared a background memorandum for this hearing that describes the documents and their significance in detail. I ask that this memorandum and the redacted versions of documents cited in the memorandum be made part of this hearing record.

The Chiron plant in Liverpool was not an ordinary FDA-regulated facility. It's a facility with a history of contamination problems that makes half of the U.S. supply of flu vaccine. The plant should have received the highest priority from FDA.

Yet the agency ignored glaring problems at the facility and missed repeated opportunities to correct them.

I have been in Congress for 30 years. Throughout this period, oversight of FDA has been one of my highest priorities. I drafted many of the major laws that the agency implements, including the Orphan Drug Act, the Hatch-Waxman Act, the Nutrition Labeling and Education Act, the Safe Medical Devices Act, the user-fee law that accelerated drug approvals, and the Food Quality Protection Act.

That's why I have become so concerned about how the agency has performed in recent years.

What we are witnessing is the dismantling of FDA's enforcement and oversight capabilities. In area after area, the agency is failing to enforce the public health laws that Congress enacted. Enforcement actions for misleading drug advertisements have dropped 70% since 2001. Enforcement actions at vaccine plants and other manufacturers of biologic drugs have dropped over 80%. Key food labeling laws are being ignored.

And there is no better example of what's wrong at FDA than its failures at the Chiron vaccine facility.

The story told in the FDA documents begins in June 2003, when a team of FDA inspectors visited the Liverpool facility and found 20 serious problems at the plant, including bacterial contamination and poor sanitary practices. The FDA experts who conducted the inspection recommended that the agency take official enforcement action against the company.

Yet this recommendation was rejected. FDA "downgraded" its response and asked the company to make only voluntary reforms.

FDA's justification for failing to cite the facility is that the agency thought conditions were improving. But conditions weren't improving; they were deteriorating. Over the next 16 months, as production at the facility increased, the problems found in June 2003 mushroomed.

Yet during this entire period, FDA never once revisited the plant to see if Chiron was correcting its problems and making safe vaccines.

Incredibly, FDA remained passive even after August 25, 2004, when Chiron disclosed that millions of doses of vaccine were contaminated by a potentially lethal form of bacteria.

A responsible regulator would have inspected the plant, demanded to review its production records, and convened high-level meetings of the agency's top experts. And that's exactly what the British regulators did. A senior British health official summed up their philosophy as, "Seeing is believing."

By contrast, FDA conducted oversight by conference call, trusting a stream of false assurances by Chiron that the plant had no serious problems. FDA conducted no inspection; it reviewed no plant records; and it was caught completely by surprise when British regulators shut down the plant on October 5.

FDA's laxity has had a heavy cost. If FDA had ensured that the problems identified in June 2003 were fixed, this year's flu crisis might never have happened. And if FDA had responded aggressively to the contamination problems in August, our public health system would have had critical extra weeks to prepare for the shortage and to avoid the chaos that ensued in October.

It is essential for FDA to learn from its mistakes. But so far, the Administration has been unwilling even to admit them. In recent weeks, the President, the HHS Secretary, and the Acting FDA Commissioner have all reassured the public that FDA did everything right. The Acting Commissioner has even indicated he would do it all over again the same way.

After the flu crisis broke, Dr. Crawford told the public that the June 2003 inspection had "no relevancy" to the problems found in 2004. He said that FDA monitored the actions of Chiron and ensured that the violations found in 2003 were corrected. And he said that the U.S. and British regulators acted "in synchrony."

None of these statements were true. In this Administration, inconvenient facts are simply ignored. This is a dangerous way to govern and it is particularly hazardous for the public health.

I expect that the Chairman may disagree with me today about the interpretation of some of the FDA documents. That's his right. But even as we disagree over specifics, I want to commend the Chairman for his approach to this hearing. He has asked for the right documents and he has worked with me to ensure that we can release redacted copies so that members and the public can judge their significance for themselves. That's exactly the right way to approach this important hearing.

I look forward to the testimony of the witnesses.

Chairman TOM DAVIS. Thank you.

I know a lot of Members would like to make opening statements, but if we go through this, we will never get to our panel; and our conference is still going on. So what I would ask is we will give Members a week to submit written statements for the record and, of course, on the questions they can make statements and use their time to do that.

We are going to move to our first panel of witnesses. Dr. Julie Gerberding, the Director of the CDC; Dr. Anthony Fauci, the Director of the National Institute of Allergy and Infectious Diseases; and Dr. Lester Crawford, the Acting Commissioner of the Food and Drug Administration. They are going to discuss efforts being taken at the Federal level to manage the flu vaccine crisis. They will also describe their efforts to coordinate distribution with State and local authorities, and what steps are being taken in preparation for next year's flu season.

It is our policy to swear all witnesses in. You have all been here before, so if you would please rise and raise your right hands.

[Witnesses sworn.]

Chairman TOM DAVIS. Thank you very much.

Dr. Gerberding, we will start with you. As you know, we have a light here. Your entire statement is in the record, and I can tell you that our staff and Mr. Waxman's staff have been through the written testimony. We would like you, if you could, to try to limit your testimony to 5 minutes. You have a light in front of you. When the light turns orange, 4 minutes are up; when it is red, 5 minutes are up. And when it is red, if you could move to completion as quickly as possible. I don't want to cut you off if you think there is something you need to say, because this is televised and people are watching, but we are conscious that we have a lot of questions and giving ample time to amplify at that point.

Dr. Gerberding, thank you for being with us. Please go ahead.

STATEMENTS OF DR. JULIE L. GERBERDING, DIRECTOR, CENTERS FOR DISEASE CONTROL AND PREVENTION; DR. ANTHONY S. FAUCI, DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES; AND DR. LESTER M. CRAWFORD, ACTING COMMISSIONER, FOOD AND DRUG ADMINISTRATION

Dr. GERBERDING. Thank you. And I thank you and the staff of the committee for their incredible interaction and professionalism in helping us prepare and be responsive to this hearing.

CDC is in a situation where we are faced with two big goals. One is to do our part to ensure that we do have a modern vaccine available to everyone who needs it that is safe, effective, affordable, and accessible, and is produced in a domestic manufacturing process that is reliable and robust. We have a second urgent goal, and that is to assure that the vaccine we do have this year gets to the people who need it the most as quickly as possible.

And I would just like to start by thanking some very important health protection heroes who have been doing their part. First and foremost, I thank the people who have been patiently waiting in lines and persistently trying to find vaccine. I am sorry that they

are in this situation. We are doing everything we can to distribute the available vaccine that is out.

I also thank the people who have stepped aside to let those who need the vaccine get it. I am incredibly appreciative of Aventis, who has collaborated with CDC's allocation plan. Aventis, Chiron and the distributors who have made proprietary information available to health officials so that we can do a good job of targeting the vaccine.

Most importantly, I thank the true heroes of this whole process, which are the State and local health officials who have been working around the clock to assess the needs, assess the flu situation in their jurisdictions, and make hard decisions about where to allocate vaccine at the local level.

On the next graphic I have a picture of the current flu situation as of the end of a week ago. The current situation is good news: the season is not off to a fast start. We have local flu activity or sporadic flu activity in many States; we still have some States with no flu activity.

But as we pointed out in the next graphic, flu is very unpredictable. The peak months of flu activity is very unpredictable. February is the most common peak, but it can be earlier or later than that. We also know that demand for flu vaccine is unpredictable. We have seen, this year, a great increase in demand. Certainly we have learned that the supply is unpredictable. The current influenza activity suggests that situation is getting us where we have a little more time to get vaccine out, but we are not resting until we have every dose allocated.

On the next graphic I have just put an organizational chart of the CDC operation. We have activated our Emergency Operation Center to handle the logistics of the flu season this year. It involves several hundred people across CDC and public health agencies who are working on various tasks. First and foremost among them is allocating vaccine. CDC is using about 20 times more dollars for flu this year than we did in 2002, so we are doing everything we can to utilize those dollars and achieve the best possible flu preparedness that we can.

In August, when we learned of the shortage, we purchased vaccine for the stockpile in addition to those doses that we had purchased earlier in the year. We also increased our supply of antiviral medication for the stockpile. And more recently, after the loss of the vaccine was noted in October, we have increased by 5 million treatment courses antivirals for the stockpile. We have also, in August, initiated a survey to assess States' preparedness and contingency planning for reprioritization and reallocation of vaccine, and took a number of steps within the agency to have some contingency for worst-case scenario. However we were operating on the premise that the most likely scenario is that ultimately we would end up with an unprecedented supply of vaccine.

On the next graphic I just have given a very few snapshots of the kind of traditional flu tracking we do at CDC. This involves people across our health agencies. We do laboratory typing, State-based typing, mortality tracing of both adults and pediatric populations.

But on the next graphic I have demonstrated some of the new innovations that we are utilizing this year that never have been used before to track flu. Chief among them is an ongoing household survey where we can assess people's vaccine status on an ongoing basis. In the first week of November, through the household survey, we were able to determine that our targeting efforts are working. Only 4 percent of low-priority patients have been vaccinated this year, and for those that need it most, including the seniors over age 65, we have more than 26 percent vaccine coverage, which is about where we would be at the midpoint of the flu season.

The last graphic really illustrates the most important component of all, and that is that flu is a preventable illness. Vaccine is the most important component of prevention, but there are other steps that we have to focus on this year as well, including prevention of person-to-person transmission, respiratory hygiene, hand hygiene, and, of course, antivirals. For people who cannot get the flu vaccine but need it, it is very important that they seek medical attention at the earliest onset of flu, because antiviral drugs can treat flu and prevent serious complications. We want to make sure that word gets out widely. And, of course, we are also preparing for a worse flu season than usual through other interventions at the community and institutional level if we need them as we go down the road.

There are a number of things ongoing across the agency, and we really appreciate the support of Congress in helping us get there. We know we need to do more. We know that we have requested $100 million in the 2005 budget to modernize our vaccine strategy, and we look forward to working with you in the committee and others on how we can do this expeditiously and successfully. Thank you.

[The prepared statement of Dr. Gerberding follows:]

Testimony
Before the Committee on Government Reform
United States House of Representatives

CDC's Influenza Vaccine Efforts

Statement of
Julie L. Gerberding, M.D., M.P.H.
Director
Centers for Disease Control and Prevention
U.S. Department of Health and Human Services

CDC
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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,

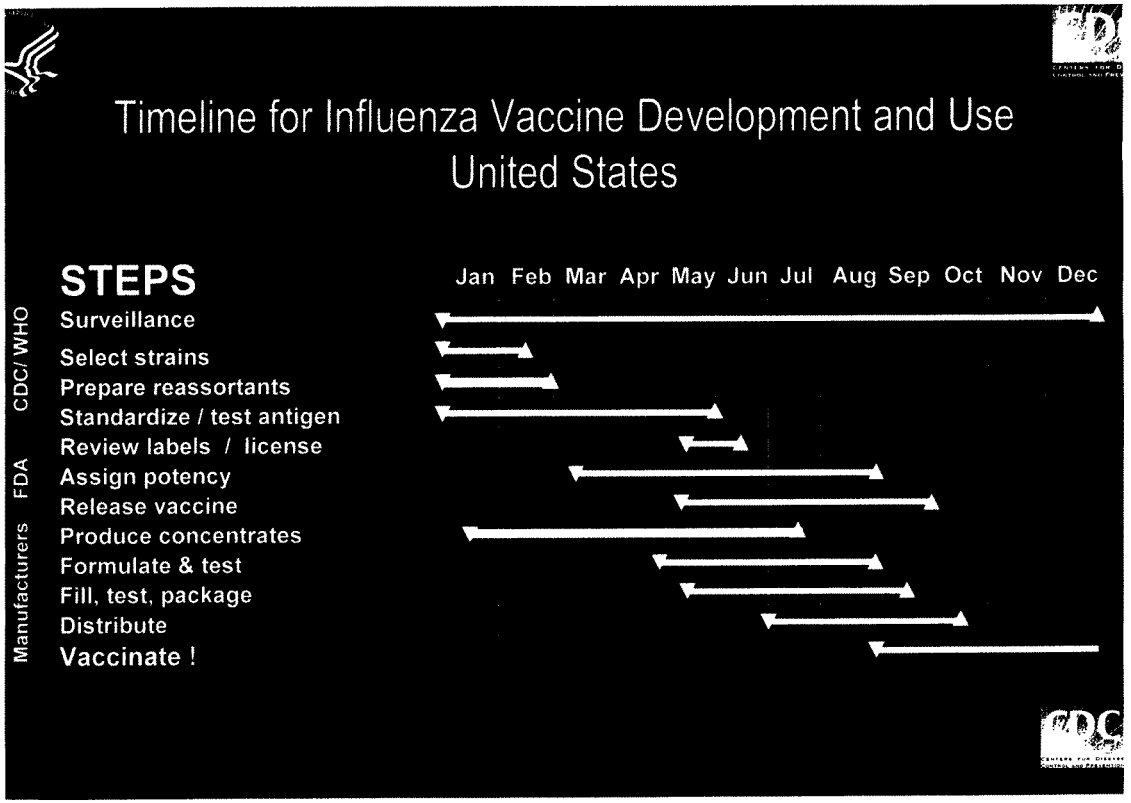
one has reported local activity, and 26 states and New York City have reported sporadic influenza activity. Twenty states and the District of Columbia have reported no influenza activity.

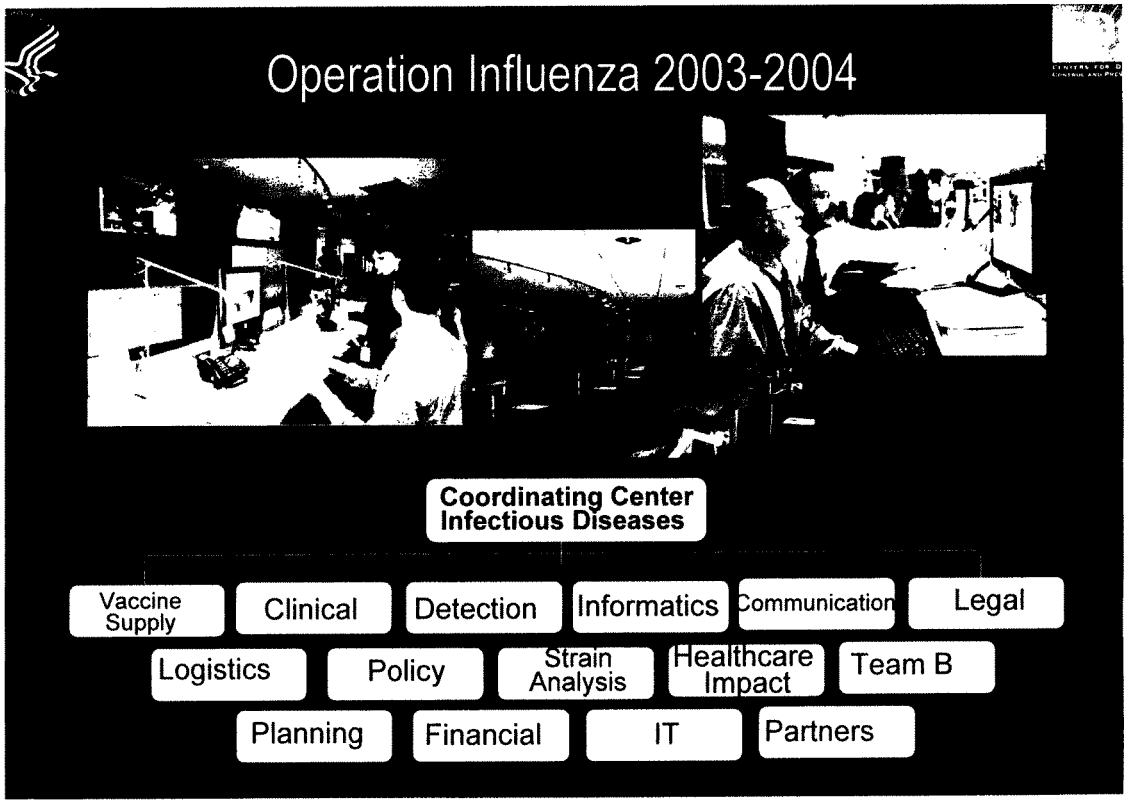
CDC has characterized three influenza viruses collected by U.S. laboratories since October 1, 2004. All were influenza A (H3N2) viruses and were characterized as A/Fujian/411/2002-like, which is an influenza component included in the 2004-05 influenza vaccine.

CONCLUSION

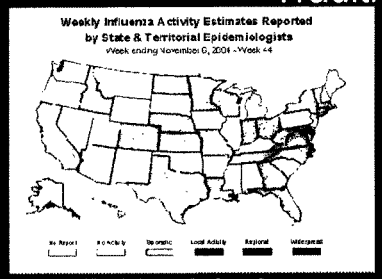
Thank you for bringing additional attention to this important public health issue. CDC is committed to protecting and promoting health for all Americans, preventing disease and disability through public health research and public outreach, and support of important interventions including vaccination. 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.

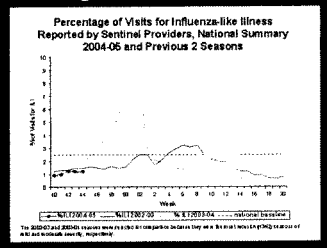

Timeline for Influenza Vaccine Development and Use
United States
STEPS
Surveillance
Select strains
Prepare reassortants
Standardize / test antigen
Review labels / license
Assign potency
Release vaccine
Produce concentrates
Formulate & test
Fill, test, package
Distribute
Vaccinate !
CDC/ WHO
FDA
Manufacturers
Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec


Operation Influenza 2003-2004
Coordinating Center
Infectious Diseases
Vaccine Supply
Clinical
Detection
Informatics
Communication
Legal
Logistics
Policy
Strain Analysis
Healthcare Impact
Team B
Planning
Financial
IT
Partners

Tracking Influenza…Targeting Preventing Traditional Strategies

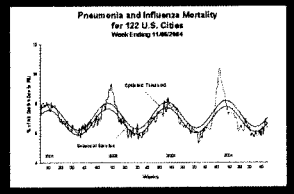


Epidemiologists:
Influenza Activity



Sentinel Providers:
Influenza-like Illness Visits

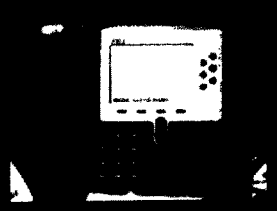
Laboratories:
Virus Typing



122 Cities: Pneumonia
& Influenza Mortality

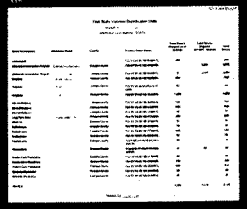
Sentinel Sites: Pediatric
Influenza Hospitalization

Tracking Influenza...Targeting Prevention
New Innovations



Household Survey:
Vaccine Use

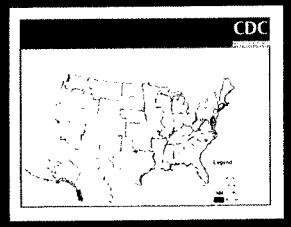
Long-term Care:
Vaccine Needs Survey



State & Local Health
Officials: Secure Vaccine
Allocation Database

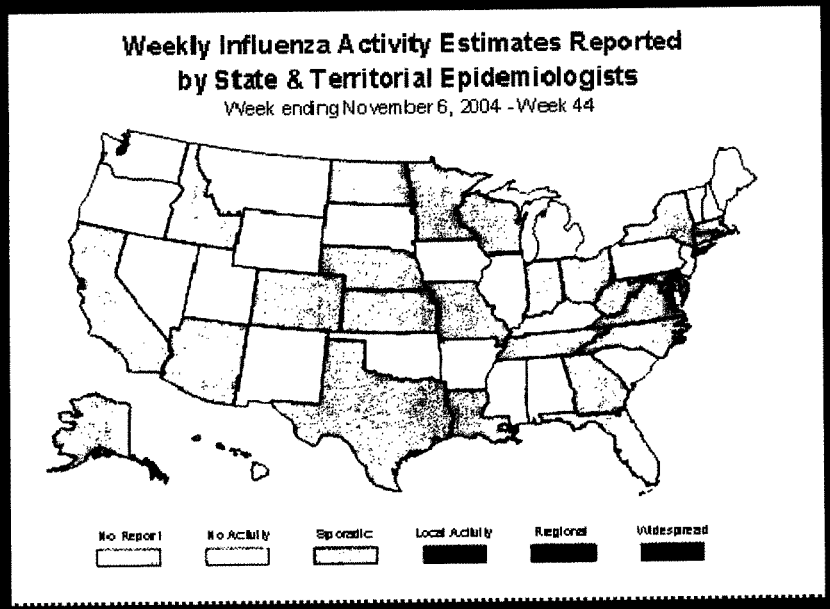
Laboratories: Virus
Genetic Sequencing
& Rapid H5 detection

Global Biodetection
Network



BioSense:
Influenza-like Clinic Visits

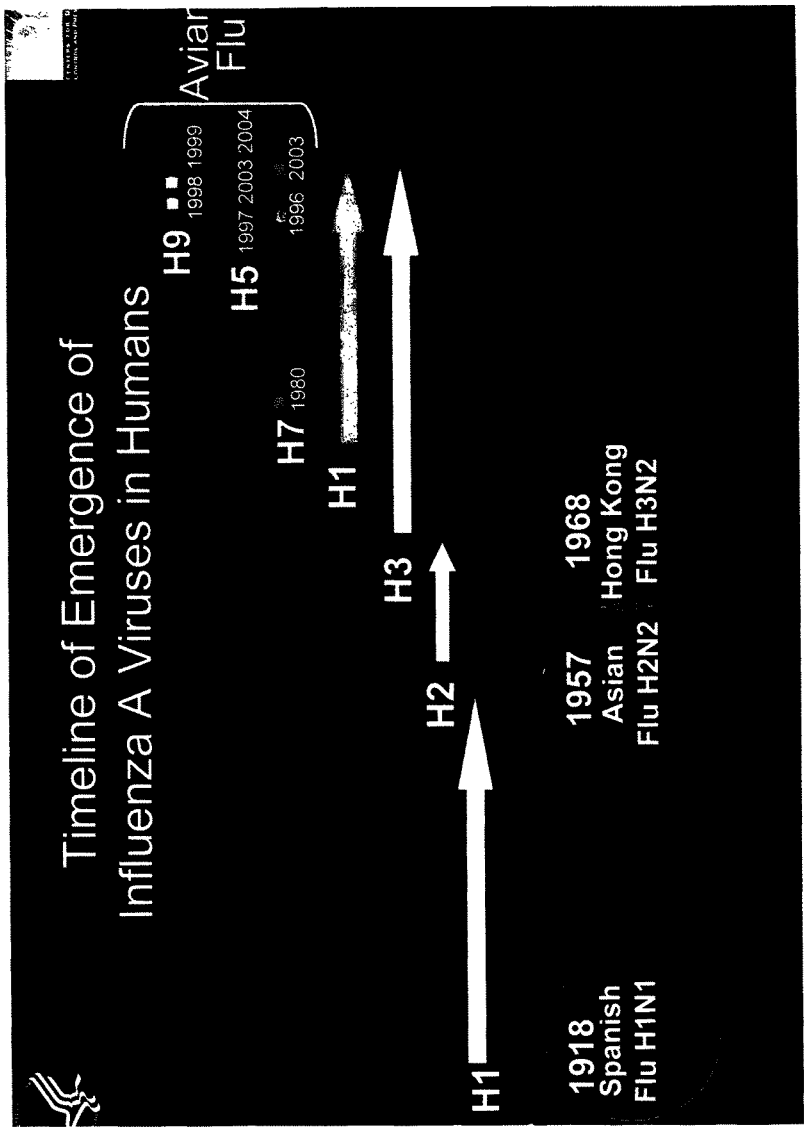
Influenza Activity: Week 44

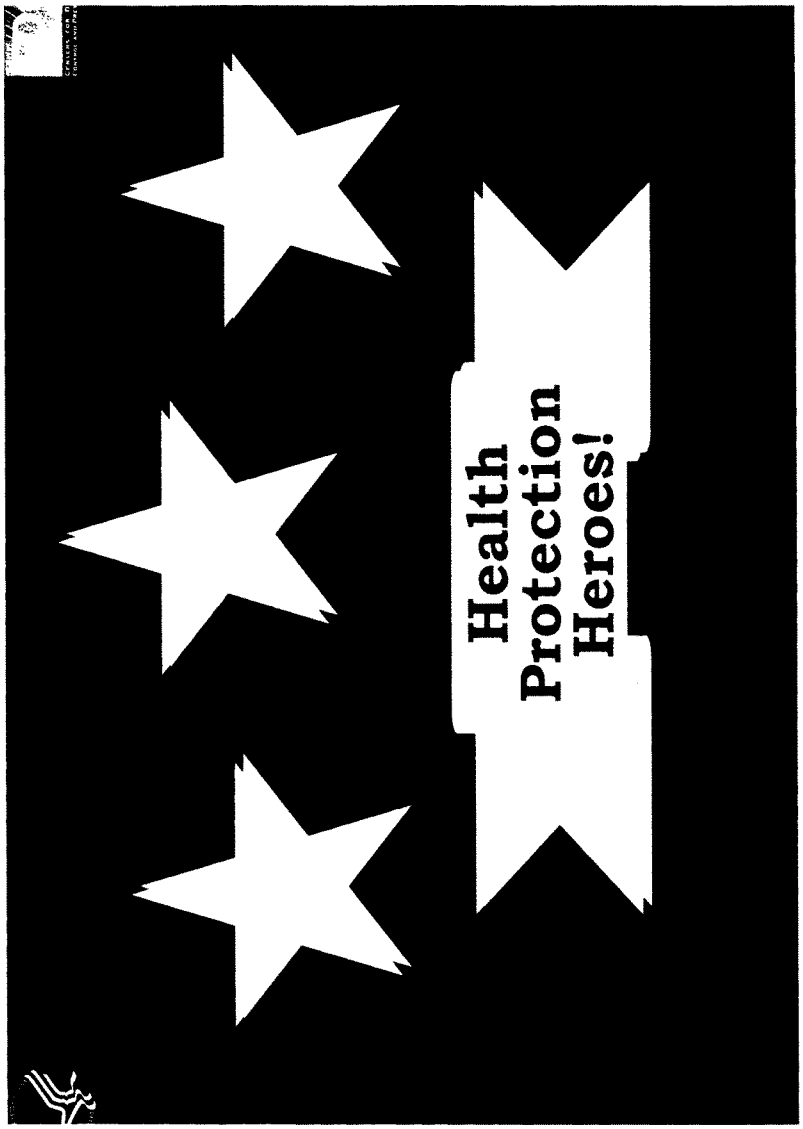


Influenza is Unpredictable:
Peak Months of Influenza Activity in Past 21 Years
Number of Years
10
9
8
7
6
5
4
3
2
1
0
4
5
9
3
DEC
JAN
FEB
MAR

Influenza is Preventable!

- Vaccination
- Respiratory hygiene
- Hand hygiene
- Stay home when ill with flu; don't send ill children to daycare or school
- Antiviral medication can prevent and treat influenza…if at risk for flu complications, contact clinician early if flu symptoms occur


Timeline of Emergence of
Influenza A Viruses in Humans
Avian
Flu
H9 1998 1999
H5 1997 2003 2004
H7 1980
1996 2003
H1
H3
H2
H1
1918
Spanish
Flu H1N1
1957
Asian
Flu H2N2
1968
Hong Kong
Flu H3N2


Health
Protection
Heroes!

Chairman TOM DAVIS. Thank you.

Before we get to Dr. Fauci, Mr. Waxman.

Mr. WAXMAN. Dr. Fauci, before we hear from you, I want to express my feelings, and I think the feelings of the members of this committee, about the loss, and sudden loss, of a leader in infectious diseases, your Deputy, Dr. John La Montagne.

Members may not have known him personally, but he was a person from whom we all benefited. He worked on issues such as flu vaccination, biodefense research, malaria, and tuberculosis. He was held in the highest esteem by all of his colleagues. He had an exemplary public service record. I know it is a loss to you, and I think to the country, that he has suddenly passed away, and I wanted to extend my condolences.

Chairman TOM DAVIS. And I concur with that.

Dr. FAUCI. Thank you very much, Mr. Waxman, Mr. Chairman, and members of the committee. We really appreciate the recognition that you have given to John La Montagne. It is a fact that John was one of the leaders in influenza vaccine research and, in fact, when he first came to the National Institutes of Health almost 30 years ago, he was the first influenza program officer in our research enterprise. So I think he would be particularly interested in this hearing were he here today, and thank you for your recognition.

Thank you, Mr. Chairman. I would like to take my time allotted to me now to talk to you a bit about the research approach toward tackling and meeting the challenge of influenza, both the immediate challenge and the long-range challenge, including that of pandemic flu.

As shown on this first poster, the NIH influenza research is one of the components of the Department of Health and Human Services' comprehensive program involving surveillance, regulation, and research to not only understand the influenza virus and the disease's cause, but also to help us partner better with industry in order to overcome some of the challenges that we have been meeting over these past several months.

The research endeavor is comprised of both basic research; research capacity; a bit of surveillance, which, as you know, is fundamentally what the CDC does; but the end point is to develop vaccines, therapeutics, and diagnostics.

This particular slide showing the influenza funding I think is very telling, because it shows the effort that has been put in under the leadership of Secretary Thompson at the Department in expanding our capabilities. As you can see, in 2001 our research endeavor was about $20 million, and the President's budget for 2005 is approximately $66 million, a clear, rather impressive increase in resources.

Some of the scientific issues that were tackled are of importance to the discussions that are taking place here today. Many of you have heard of the terminology "reverse genetics." I will try to simplify that for you.

This was a technique that was developed by NIH grantees, and what this technique does, it takes some of the uncertainty out of finding and isolating the seed virus to grow for a vaccine. And when you get a virus like isolated this year, the H5N1 from Asia,

and you want to grow that to develop a pilot lot, you generally put a vaccine that is well adapted to growing in eggs, which is the main medium of growing, together with the vaccine in question, hoping that they will naturally reshuffle their genes so that you have the component of the virus in question within the framework of a virus that you know from year after year grows well.

Reverse genetics circumvents that; it allows you to actually pick out the genes and deliberately put them together to form a hybrid type of a virus that we call a reassortment, a molecular version of the reassortment, where you deliberately do it yourself. That is how we isolated and got the H5N1 that we are now preparing for a vaccine in the event of a pandemic flu.

The next slide shows the two major research endeavors that are ongoing now to tackle the question of how we can have alternatives to egg-based vaccine, and that is the development of cell culture vaccine production and recombinant DNA technology. Hopefully we will get a chance to discuss this during the question period.

Another important component of tackling influenza is what we do with therapies, therapies that are for the actual treatment of influenza as well as those that can be used for prophylaxis or prevention. There are four drugs that are available today against different targets. Three of them are used for prevention and all of them can be used for treatment.

We need a more robust pipeline to be able to have in our armamentarium other drugs in the event of the development of resistance to these drugs by the influenza virus. And we know from experience that whenever you treat a microbe over a period of time, sooner or later there will be resistance. But we do have drugs, as was mentioned by Dr. Gerberding, such as Tamiflu and Rimantadine in our strategic national stockpile, with in fact many more doses now being prepared for that stockpile.

And finally let me just mention a word of how we use the research enterprise to approach the pandemic flu threat that is an ever-looming threat. We know that this is occurring in Asia right now. H5N1 is a virus that has already infected 44 people and killed 32. The good news is that it has not yet learned to effectively transmit from person to person; there is only one documented case.

But if we use history to tell us what microbes can do, sooner or later either this virus or a related virus might learn that. So there are some research issues that need to be addressed that will help us to be able to meet that challenge.

They are listed here. One is to isolate that virus, which we, in collaboration with the CDC and the WHO, last year did, and we did it by the reverse genetics technique that I introduced you to just a moment or two ago. We are developing pilot lots of the H5N1 and other bird flus. By pilot lots we mean small amounts, 8,000 to 10,000, that can be used in clinical trials, as shown on the third bullet.

Those clinical trials will begin anywhere from January up to and including March or April; and this has been in association with the purchase by the Department of 2 million doses of H5N1 from Aventis-Pasteur to be able to have in our stockpile, should we need it. And, finally, the continual screening and development of new therapeutics.

So, in summary, as part of the broad comprehensive approach of the Department, the NIH research endeavor will hopefully continue to contribute productively to the challenge that we will inevitably meet. Thank you, Mr. Chairman.

[The prepared statement of Dr. Fauci follows:]

Testimony
Before the Committee on Government Reform
United States House of Representatives

The NIH Biomedical Research Response to Influenza

Statement of
Anthony S. Fauci, M.D.
Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
U.S. Department of Health and Human Services

For Release on Delivery
Expected at 1:00PM
Wednesday, November 17, 2004

Mr. Chairman and Members of the Committee, thank you for the opportunity to discuss with you today the role of the National Institutes of Health (NIH) in helping to ensure that the nation has a reliable supply of safe and effective influenza vaccines.

Because the influenza viruses in circulation change somewhat from season to season, the U.S. supply of influenza vaccine must be renewed each year – and often contains flu viruses that are different from those used the previous year. The current technology for vaccine manufacture requires that key decisions, such as which viruses will be included and the number of doses needed, be made many months before the arrival of the influenza season. The serious vaccine shortage that has occurred this year underscores the difficulties we face in annually renewing the influenza vaccine supply, and highlights the pressing need to move toward adoption of a variety of vaccine manufacturing techniques that include newer technologies that may decrease the risk involved in vaccine production as well as improve flexibility and the speed at which the vaccines can be made.

The National Institute of Allergy and Infectious Diseases (NIAID), a component of NIH, is the lead agency for the conduct of research on all infectious diseases, including influenza. In that capacity, NIAID provides the scientific input required to facilitate the development of both new influenza vaccine technologies and novel antiviral drugs against influenza viruses.

Under this administration we have made tremendous progress. 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. Total NIH funding for influenza research has grown more than three-fold in recent years, from $20.6 million in FY 2001 to a requested $65.9 million (320 percent) in the FY 2005 President's Budget. This is part of the largest investment ever made by the federal government in protecting against the flu.

NIAID Influenza Research

NIAID pursues an ambitious basic and applied research agenda on influenza, including viral biology, pathogenesis, host immune responses, and epidemiology, which underpin our many programs that are aimed at developing new and improved influenza countermeasures such as vaccines, therapies and diagnostic tools. Because influenza vaccines are the primary public health tools available to limit the disease burden caused by annual influenza epidemics, vaccine research has a very high priority. NIAID also supports several research activities specifically focused on identifying and countering any future influenza pandemic.

Basic Research

The development of new and effective influenza countermeasures rests on a foundation of basic research. Some basic research focuses on specific questions regarding the biology of the virus such as how it enters cells, replicates, mutates, evolves into new strains and induces an immune response, while other projects can be more broadly applied. For example, under a recent NIAID initiative called the Influenza Genome Project, NIAID will collaborate with researchers around the world to obtain the complete genetic sequence of several thousand human and animal influenza viruses. The resulting library of influenza sequences, some of which may be derived from samples collected decades ago, should add greatly to our understanding of what makes one strain more lethal than another, what genetic determinants most affect immunogenicity, and how the virus evolves over time. All of this is precisely the kind of information that will significantly enhance our ability to create more effective countermeasures.

Vaccines

Because influenza is such a highly transmissible virus, vaccines are essential tools for the control of influenza epidemics. The current system for the production of U.S. licensed influenza vaccines uses fertilized chicken eggs to grow influenza vaccine strains that have been selected to match the viruses likely to circulate in the coming influenza season. The viral particles are purified from the eggs, inactivated, and processed for distribution.

Although the egg-based technology has served us reasonably well for more than 40 years, there are several limitations to the current system that include: (1) a lengthy manufacturing process; (2) the need to forecast and select the virus strains to be used in the vaccine at least six months in advance of the influenza season; and (3) the annual need for hundreds of millions of fertilized chicken eggs to manufacture the vaccine. The decisions about which viral strains to include in the vaccine may not always be correct, but the long lead time required to acquire eggs for vaccine production makes mid-course corrective action virtually impossible. Additional limitations include the fact that some people are allergic to eggs and therefore cannot receive the classic vaccine. In addition, some influenza viruses do not grow well in chicken eggs and may in fact be virulent for the eggs, a circumstance that may result in delays bringing a vaccine to market and a possible decrease in the total number of doses available.

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.

NIAID supports several research projects and other initiatives intended to foster the development of new influenza vaccines and manufacturing methods that are simpler, more reliable, yield more broadly cross-protective products, and provide more protection than those currently in use. For example, a technique developed by NIAID-supported scientists called reverse genetics allows scientists to manipulate the genomes of influenza viruses and to transfer genes between viral strains. The technique allows the rapid generation of seed viruses for vaccine candidates that exactly match the anticipated epidemic strain. By removing or modifying certain virulence genes, reverse genetics also can be used to convert highly pathogenic influenza viruses into vaccine candidates that are safer for vaccine manufacturers to handle.

To encourage participation by the pharmaceutical industry, NIAID supports Challenge Grants to fund the development of new influenza vaccine technologies. One approach under active development is the use of cell cultures to grow vaccine strains, rather than eggs. Another approach is to genetically engineer baculovirus, an insect virus not related to influenza, to express a gene that encodes an influenza coat protein such as hemagglutinin or neuraminidase. The engineered baculovirus is then grown in insect cell cultures, and the influenza protein that the virus produces is purified for use as a "recombinant subunit" influenza vaccine. A recent NIAID-supported Phase II clinical trial of a vaccine produced by Protein Sciences Corporation using this strategy showed that it is well tolerated and immunogenic; the company is conducting further

clinical evaluation of this product. Other new pathways for producing influenza vaccines include DNA-based approaches and the development of broadly protective vaccines based on influenza virus proteins that are shared by multiple strains.

NIAID has been very successful in the past with ground-breaking vaccine research, including scientific advances that led to the development of hepatitis B, *Haemophilus influenzae b*, pneumococcal pneumonia, acellular pertussis, and live-attenuated intranasal influenza vaccines. I am confident that the approaches that we are currently pursuing with influenza will lead to a next-generation vaccine that improves upon the current egg-based technology.

In addition to developing influenza vaccine candidates, NIAID has developed an extensive capacity for clinically evaluating these products. For example, NIAID's Vaccine and Treatment Evaluation Units (VTEUs) comprise a network of university research hospitals across the United States that conduct clinical trials to test candidate vaccines for infectious diseases. These units can be accessed by both academic and industrial vaccine developers to evaluate the safety, immunogenicity, and ultimately, the efficacy of candidate vaccines.

Therapeutics

Antiviral medications are an important counterpart to vaccines, both to treat infection after it occurs and to prevent illness after exposure; four drugs are

currently available for the treatment of influenza, three of which are also licensed for prevention. NIAID actively supports identification of new anti-influenza drugs through the screening of new drug candidates in both cell culture and in animals. In the past year, seven promising candidates have been identified. Efforts to design drugs that precisely target viral proteins and inhibit their functions also are under way. In addition, NIAID is developing novel broad-spectrum therapeutics against many influenza virus strains; some of these target viral entry into human cells, while others specifically attack and degrade the viral genome.

Pandemic Influenza

Although the impact of influenza on morbidity and mortality in a normal epidemic year is substantial, much more serious influenza pandemics also can occur. As influenza viruses spread, they continuously evolve and accumulate small changes in their outer coat proteins, a process called "antigenic drift." This occurrence allows the virus to at least partially escape the human immune responses primed by vaccination or exposure to earlier versions of circulating influenza viruses. Influenza viruses can also jump species directly from certain animals such as chickens to human as well as swap genes with influenza viruses that infect birds, chickens, pigs, or other animals; the latter process is referred to as "reassortment". When such reassortment events occur, the result is the replacement of one or more of the outer coat proteins of the human virus with that of the animal virus, or an "antigenic shift." If the virus that has jumped species or the new reassorted virus evolves to be efficiently transmitted between

people, a deadly influenza pandemic can result. As the population acquires immunity to the new strain over the next several years, the pandemic strain fades into the routine background of circulating viruses.

Three influenza pandemics occurred in the 20th century, in 1918, 1957, and 1968. The pandemic that occurred in 1918-1919 was the most severe, killing 20-40 million people worldwide, including more than half a million individuals in the United States. The pandemics that began in 1957 and 1968 killed approximately 2 million and 700,000 people worldwide, respectively.

One of the first internal committees Secretary Thompson created when he came to HHS was on pandemic flu. And last August, the Secretary unveiled the Department's draft Pandemic Influenza Response and Preparedness Plan. This plan outlines a coordinated national strategy to prepare for and respond to an influenza pandemic.

NIAID conducts research to understand the viral biology and epidemiology that underpinned past pandemics, and funds an extensive surveillance network in Asia to detect the emergence of influenza viruses with pandemic potential. In addition, the draft U.S. Pandemic Influenza Preparedness and Response Plan describes specific roles for NIAID should a pandemic occur. Foremost among these is to help develop and produce an effective vaccine as rapidly as possible. Specifically, NIAID will help to characterize the newly emerging influenza strain,

isolate candidate vaccine seed viruses, develop investigational batches of candidate vaccines, and produce and distribute research reagents for use by vaccine researchers in academic and pharmaceutical industry laboratories. NIAID will also work with industry to produce and clinically test pandemic influenza vaccines at different doses and in different populations in our vaccine clinical trials sites, and will coordinate closely with CDC, FDA, and WHO to provide a safe and effective vaccine to the public as quickly as possible.

In recent years, several avian influenza virus strains that can infect humans have emerged. In 1999 and 2003, an H9N2 influenza strain caused illness in three people in Hong Kong. The H5N1 "bird flu" virus, first detected in humans in 1997, infected at least 44 people and killed 32 in 2004, and has spread widely among wild and domestic birds. There has been at least one documented case of human to human spread of an H5N1 virus. NIAID already has taken several steps to develop vaccines against both of these potential pandemic strains. To address the H9N2 threat, NIAID contracted with Chiron Corporation to produce investigational batches of an inactivated vaccine, which will be evaluated clinically by NIAID early next year. For H5N1, Aventis-Pasteur, Inc. and Chiron are both producing investigational lots of inactivated H5N1 vaccine preparations; additionally, DHHS has contracted with Aventis to produce up to 2 million doses to be stockpiled for emergency use, if needed, to vaccinate health workers, researchers, and, if indicated, the public in affected areas.

Development and evaluation of a combination antiviral regimen against these potential pandemic influenza strains are also now under way.

Transforming the Flu Vaccine Marketplace for 21st Century

President Bush has invested more in research, development and acquisition of flu vaccines and medicines than any President in our nation's history in an effort to revitalize a deteriorated flu vaccine marketplace and better protect the American people.

Conclusion

Given the disruption of the influenza vaccine supply that we experienced this year, and the inherent difficulties associated with the current manufacturing technology, it is clear that we must move toward next-generation influenza vaccines with all deliberate speed. NIAID's role in influenza vaccine development is to carry out the research upon which these new vaccines will be based, and to forge productive partnerships with private sector pharmaceutical and biotechnology companies to speed development and clinical evaluation of promising candidates.

In closing, Mr. Chairman, I would like to take a moment to remember John R. La Montagne, Ph.D., deputy director of NIAID, who died suddenly on November 2 while traveling to a meeting of the World Health Organization in Mexico City. Throughout his almost 30-year career at NIH, John's leadership

and commitment to improving global health, particularly in the arena of influenza vaccine research, were remarkable. His generosity, wit, even-handedness and kindness made him a friend to all who knew him. Personally, he was a dear friend and one of the finest people I have ever known. He will be sorely missed.

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

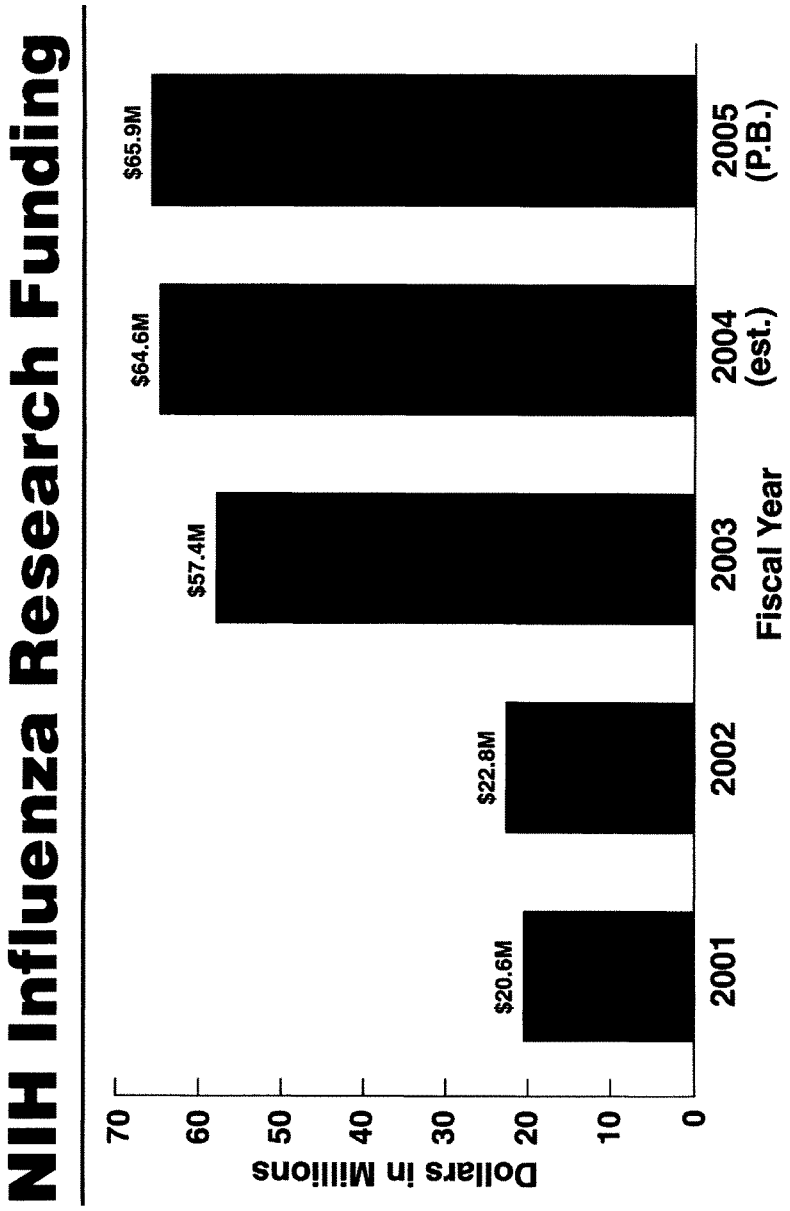
House Committee on Government Reform

United States House of Representatives

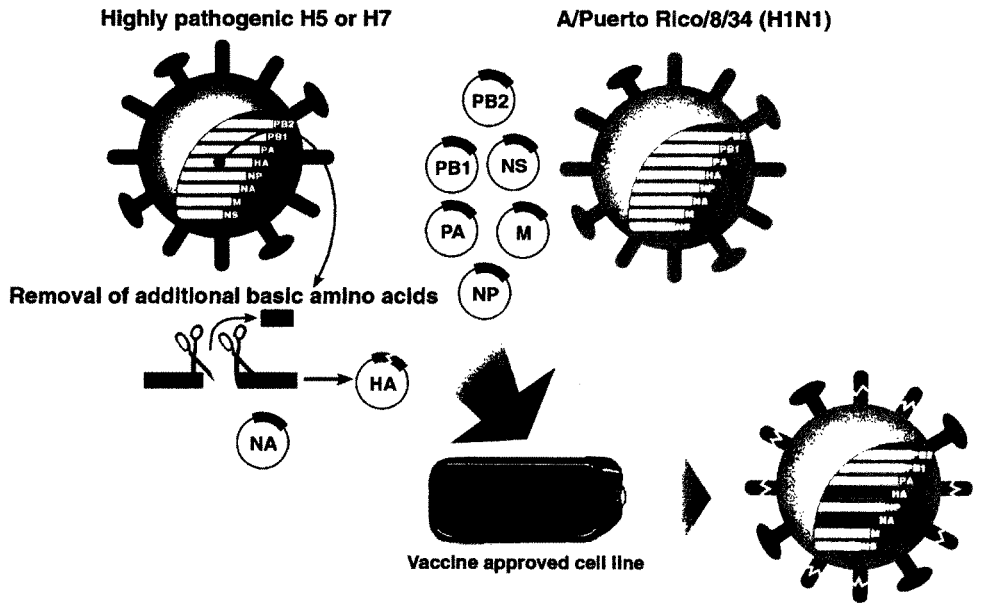
Anthony S. Fauci, M.D.
Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
U.S. Department of Health and Human Services

Tuesday, October 17, 2004

NIH
Influenza
Research
Diagnostics
Expansion of
Research
Capacity
Therapeutics
Basic Research
Vaccines
Surveillance
and
Epidemiology


NIH Influenza Research Funding
Dollars in Millions
0
10
20
30
40
50
60
70
$20.6M
$22.8M
$57.4M
$64.6M
$65.9M
2001
2002
2003
2004 (est.)
2005 (P.B.)
Fiscal Year

Influenza Vaccine Seed Virus Production Using a Reverse Genetics System

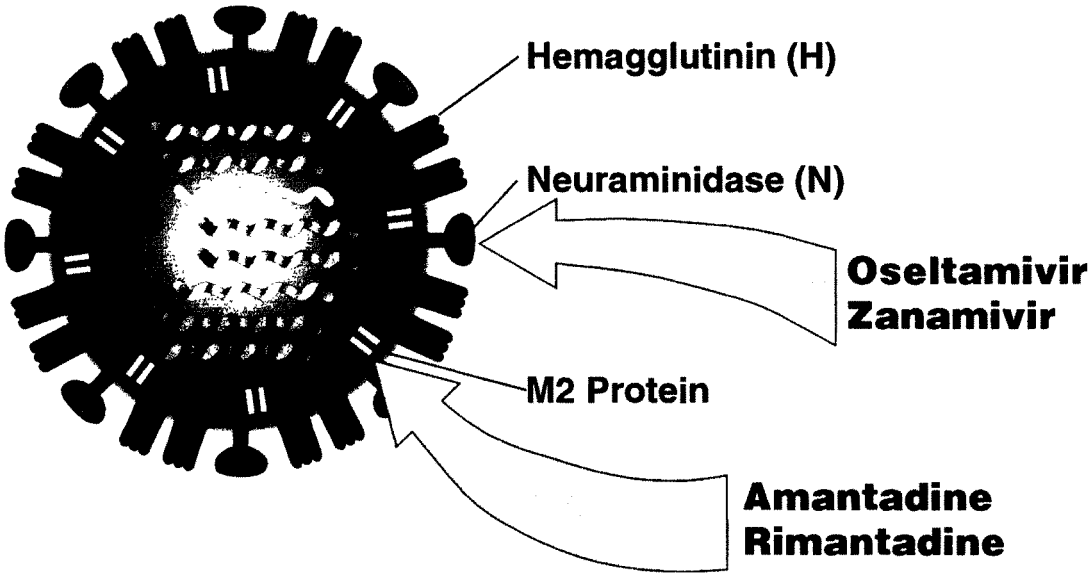


Source: Webster et al: *Vaccine* 20:3165 (2002); Science 302:1519 (2003)

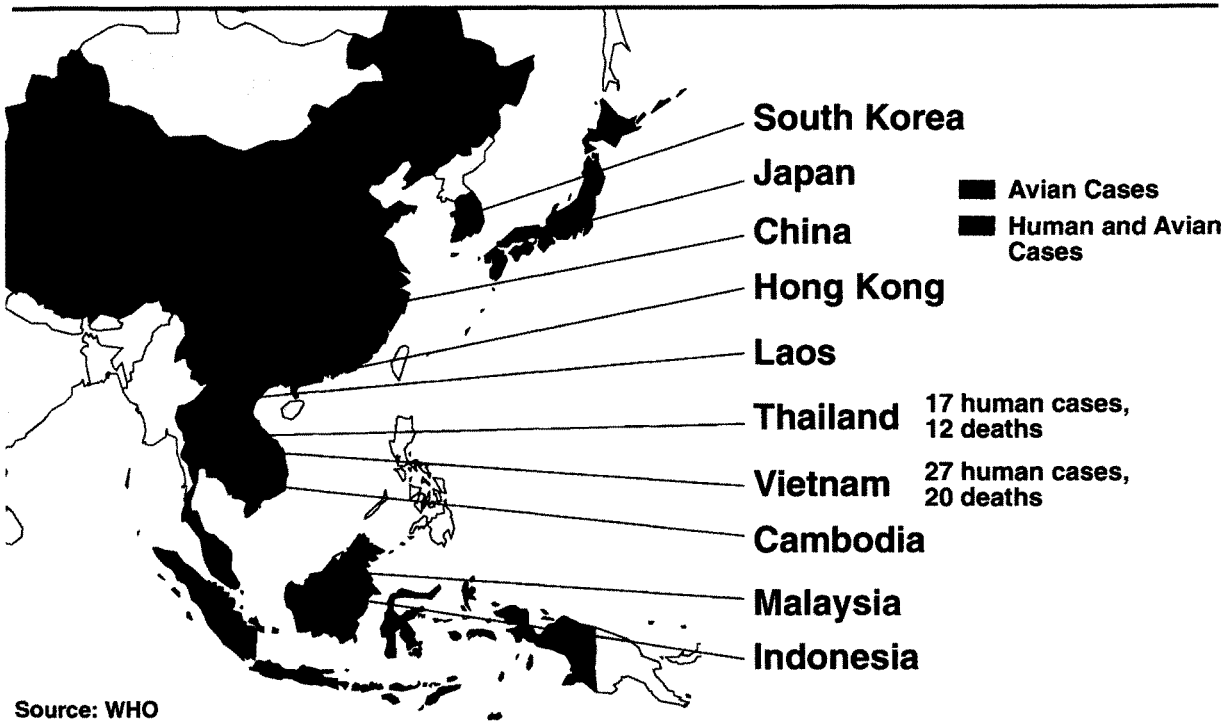
Alternatives to Egg-Based Influenza Vaccine Production

- Cell culture-based vaccine production
- Recombinant DNA methods

Antiviral Therapies for Influenza



H5N1 Influenza in Asia, 2004



Source: WHO

NIH Activities in Preparation for Pandemic Influenza

- Isolation of seed virus by reverse genetics
- Development of vaccine pilot lots for clinical trials
- Execution of vaccine clinical trials
- Screening and development of new therapeutics

Chairman TOM DAVIS. Thank you very much.

Dr. Crawford, thank you for being with us.

Mr. CRAWFORD. 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 supply, and advised that they were already investigating the problem to determine the root cause of the contamination. At the same time, they proceeded to quarantine all of the vaccine lots while they retested the product.

In September 2004, FDA, CDC, and Chiron scheduled weekly conference calls to discuss the status of the firm's investigation. During these calls, they advised FDA that they had identified the cause of the contamination, that it was confined to specific vaccine lots. During their investigation, Chiron informed FDA that the results of the retesting were negative. They planned to submit a final investigative report to FDA during the week of October 4th.

It is important to recall that on September 28th Chiron's chief executive officer advised the Senate Special Committee on Aging, "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."

On the morning of October 5, 2004, the British regulatory organization, MHRA, announced a 3-month suspension of Chiron's license to manufacturer influenza vaccine. FDA had no prior knowledge of that intention, to suspend the firm's license. The chief executive of MHRA indicated that they did not have the legal authority to notify FDA before the October 5th suspension.

Upon learning of the suspension, FDA contacted both Chiron and the MHRA. Chiron indicated to FDA that it believed it had satisfactorily addressed MHRA's inspectional findings. However, the British expressed serious concerns about Chiron's vaccine stocks and the company's ability to assure the safety of the vaccine. FDA immediately dispatched a senior team of scientists to the U.K. to meet with company officials and MHRA, and to inspect Chiron's Liverpool manufacturing facility.

On October 15, 2004, after completing its inspection, 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 the 2004–2005 flu season.

In coordination with others at the Department of Health and Human Services, we have been actively exploring all viable options to secure additional dosage 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 season. We have also 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.

Next year, Aventis-Pasteur believes they have the capability of producing the same or more doses of the influenza vaccine. In addition, MedImmune has indicated that it has the capability to produce 10 million doses of FluMist for the 2005–2006 season and as much as 40 million doses by 2007.

In partnership with the MHRA, we will continue to work with Chiron in an effort to bring them back online for next year's flu vaccine production. We are also encouraging foreign licensed manufacturers to apply for U.S. licensure, and we will work to help them achieve this goal.

Looking further ahead, we must develop more efficient ways to produce flu vaccine so that we have the flexibility to deal with shortages or unexpected problems. The Department has requested $100 million for fiscal year 2005 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, and we are encouraged by the positive response from Congress on this important request.

To help manufacturers overcome challenges such as the vaccine development problems that Chiron is experiencing, FDA has been investing its energy and resources in important initiative such as the Current Good Manufacturing Practices for the 21st century initiative, or the GMP initiative. Under that 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 and avoid the problems such as those Chiron experienced.

Thank you very much.

[The prepared statement of Mr. Crawford follows:]

Testimony
Before the Committee on Government Reform
United States House of Representatives

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

Statement of
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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 maximize the use of FluMist and Defense agencies will allow HHS to purchase 200,000 doses of injectable vaccine for which they had originally contracted so that we can make it available to the high-risk population in the U.S.

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.

Chairman TOM DAVIS. Thank you very much.

Mr. Waxman and I have agreed to begin the questioning. We will take 15 minutes and then Mr. Waxman will get 15 minutes on his side, and then we will go down and allow individuals to get their 5 minutes, should they desire to do so.

Dr. Crawford, let me start the questioning. FDA provided the committee with the Form 483s from the June 2003 and the October 2004 inspections of Chiron's Liverpool facility. This is an important point because a lot of has been made about a duty, perhaps, of the FDA to have gone back and continued to inspect that plant prior to October 2004.

Could you explain the differences between these two forms and why, even though some similarities exist between faults that were found in the June 2003 inspection and October 2004 inspection, that Chiron's license suspension in October 2004 was not foreshadowed by the June 2003 inspection?

Mr. CRAWFORD. Well, the two events were unrelated. In 2003 we inspected the plant and were involved with it, and we did issue Form 483, which cites some corrections that must and should be made; and the plant responded affirmatively. We were able to interact with them in a productive way; and the proof of that was that the 2003 vaccine production was completed on schedule and none of it was condemned, as was the case in 2004.

So they are two entirely separate situations. The 2004 situation was quite different.

Chairman TOM DAVIS. When the team biologics returned to the United States after its June 2003 inspection of Chiron's Liverpool facility, it initially recommended that official action be taken against the facility. FDA ultimately decided that voluntary action should be taken. Can you explain to us the protocol FDA follows in deciding actions after routine inspections of manufacturing facilities?

Mr. CRAWFORD. Yes. The inspectors that actually do the evaluation onsite come back and make a recommendation as to what kind of action FDA should take, if any, and then team biologics actually has a decisionmaking process so that all of the members of the team are able to evaluate the severity of the situation and also what progress is being made. By that time, they did have the response from the company to the 483, and based on that, and also based on the fact that vaccine production process last year did come to full and successful completion, the action was changed from mandatory to voluntary.

Chairman TOM DAVIS. FDA's routine protocol, as I understand it, is to inspect foreign manufacturers once every 2 years?

Mr. CRAWFORD. That is correct.

Chairman TOM DAVIS. The last routine inspection of Chiron's Liverpool facility, then, was June 2003. FDA informed the committee it accepted Chiron's response plan to correct the issues that were raised in June 2003 and, therefore, the file was closed on September 3, 2003, is that correct?

Mr. CRAWFORD. That is correct.

Chairman TOM DAVIS. If these steps were following standard FDA protocol, would there be a reason for FDA to go back to Chiron's Liverpool facilities prior to the 2-years time to reinspect?

Mr. CRAWFORD. No, we don't do that.

Chairman TOM DAVIS. So you were following protocol.

Mr. CRAWFORD. Yes.

Chairman TOM DAVIS. Let me just ask you this. In retrospect, now that we have seen what happened, is there anything in inspection in that time period that might have shown that we should have gone back? I know it wasn't within protocol.

Mr. CRAWFORD. No. Within the number of years that we have been doing this, for decades, this has been our standard protocol. It is modified somewhat from time to time in order to deal with the good manufacturing practices, as practices within the industry change, but the sequence of events has been unchanged over recent years and has been very effective. This is the first time we have had contamination in final lots of vaccine at that plant, and that was a different kind of thing. But we would not have changed the protocol leading up that.

Chairman TOM DAVIS. You believe that the causes of the contamination in the vaccine in October 2004 were unrelated to the initial reports that we got back in June 2003 and potential contaminations at that point?

Mr. CRAWFORD. Yes. The flu vaccine composition is changed each year based on the expected strain, so this was an entirely different production.

Chairman TOM DAVIS. Now, let me step ahead a little bit and try to understand that everyone's goal this year, MHRA, Chiron's, the FDA, is to get Chiron up and running so that they can produce flu vaccine next year. They have gone ahead and ordered the eggs; the invested financially in being able to go ahead next year and get the doses up and the supply ready for the United States.

But if Chiron isn't up and operating, if something goes wrong, if the changes that they are making within their planned operation somehow do not pass muster and we still have contamination, can you tell the committee what is our Plan B?

Mr. CRAWFORD. Well, at that point it will be early enough for us to seek alternative production facilities, but also alternative sources of vaccine from other countries and elsewhere. So that will be a signal to both the British and to us that we need to work with their version of the Centers for Disease Control and our version of our own CDC in order to work together to secure an adequate vaccine supply from other sources, if in fact they are not going to be able to provide it.

As you recall, we testified in 2002 that the vaccine industry was extremely fragile; we would be down to a very few suppliers, and we needed to work on that. When you find out too late in the production season, it is too late to seek alternative sources because they can't get up and running fast enough. It will be earlier than that this year.

Chairman TOM DAVIS. You also have foreign license manufacturers. In fact, Chiron has other plants, do they not, where they manufacture vaccine?

Mr. CRAWFORD. They do.

Chairman TOM DAVIS. Are we in the process of going out to other manufacturers that are currently providing dosage for Europe and for other parts of the free world, and have met criteria in other

countries, to get those licenses as well, so that, should this occur again, we have other sources of supply?

Mr. CRAWFORD. Yes. I have personally talked to every chief executive officer manufacturing flu vaccine anywhere in the world, even those that have elected not to come to the U.S. market, and have encouraged them to do that and also have encouraged them of the commitment of FDA to work with them in that process, because we need more competition, if you will, within the flu vaccine industry. I have also talked to the manufacturers of substances like FluMist and also the antiviral drugs, and have assured them also of our commitment. Some of them, the antiviral drug manufacturers, also have chosen to not enter the U.S. market. I have encouraged them to rethink that, and we are having a continuing series of calls on a virtually daily basis in order to see what their thinking is and also to work with them.

Chairman TOM DAVIS. It is true that worldwide there is a shortage of flu doses? It is just that in the more affluent parts of the world we tend to be able to go out and buy it and usually have ready supply? Is that a fair comment?

Mr. CRAWFORD. Yes. Dr. Gerberding would be better able to talk about that, but we consume more than our share of the flu vaccine that is produced worldwide. That is as it should be; we have a very aggressive public health program thanks to CDC, and we are moving forward, I think, to vaccinate an even larger percentage of our population. But the number of companies that are actually manufacturing are down really to about three or four.

Chairman TOM DAVIS. Dr. Gerberding, is that an accurate statement?

Dr. GERBERDING. That is accurate. I don't have the global production figures this year—we can get them for the committee—but in most years it is less than the total of 300 million doses globally.

Chairman TOM DAVIS. OK. What is the annual death toll from influenza around the world? We know it averaged about 36,000 in the United States in an annual basis. What would it be worldwide, any idea?

Dr. GERBERDING. We don't have accurate estimates globally because there really is no system for surveillance for flu deaths on an international basis.

Chairman TOM DAVIS. In many countries.

Dr. GERBERDING. We are working on that, but I can't answer the question.

Chairman TOM DAVIS. OK.

Let me go back to you, Dr. Crawford. What are Chiron's obligations to FDA in order to get their license back to produce Fluvirin vaccines for next year's flu season, and how are you working with Chiron and the MHRA to develop and implement the remediation plan, and how confident are you that we are going to be successful?

Mr. CRAWFORD. Thanks to an agreement that has been reached between the MHRA, FDA, and Chiron, we are now able to share information and also to work together in helping to get the vaccine production facilities——

Chairman TOM DAVIS. And that is the first time we have had that, correct?

Mr. CRAWFORD. It is, yes.

Chairman TOM DAVIS. In fact, without that, under British law, they couldn't share this with you.

Mr. CRAWFORD. They could not and did not share information. We are now working hand-in-glove to get that particular plant up and functioning, and a decision will be made on that by January 5. Now, it is important to note that since the facility is in the United Kingdom, the license will come from the British Government.

Chairman TOM DAVIS. Correct. And we have talked about the Plan B, that at that time you still have time to look worldwide into other areas.

Mr. CRAWFORD. Yes.

Chairman TOM DAVIS. Let me ask you another thing. We have some jurisdictions, State of Illinois, city of New York, that are talking about importing vaccines from countries that are not FDA certified.

Mr. CRAWFORD. Yes.

Chairman TOM DAVIS. What are we doing about that?

Mr. CRAWFORD. Some Governors and mayors have come to FDA and have offered to go and try to find vaccine that is still unused in wholesale distribution channels, and they have found, starting with the Governor of Illinois and then the last one to enter the situation was the mayor of New York City, they have come up with up to 750,000 extra doses. And what we are doing now is we had to first collect the lot numbers on those doses in order to be sure that they were legitimate, that they came from the plant where they were supposed to have come from. The second this is now we are developing what is called a pedigree, and that is to be sure that we know where all this vaccine has traveled throughout the world and whether or not the cold chain, as it is called, that is, refrigeration, has been in place sufficiently and adequately to make sure that the vaccine is still viable and can be used.

We are down to that point now, and we are also meeting with that CEO on a regular basis as they help us to get the data we need in order to bring the vaccine in. Now, it is not approved in the United States, so we will have to do some special procedures in order to bring it in, but we are not at that point yet, but we are making progress.

Chairman TOM DAVIS. And I would just emphasize, from my perspective, for next year and the years after, we just need to get more providers out there. And if we can't get them to produce it here, we have to go worldwide to just get them certified, where they can do that.

Also the FluMist, are we looking at testing that to see if that can have a wider applicability than it has?

Mr. CRAWFORD. Well, as I mentioned, they are going up to 10 million doses, and as you also know, it is now used for people that are in healthy physical condition between the ages of 5 and 49. The company has released information that they are interested in perhaps expanding that perhaps to some further ages, and I can assure you, although we can't reveal the procedures and what is going on in terms of the data that has been submitted to us and the relevant applications, we will do everything we can to work

with them or anyone else who wants to expand a flu vaccine product in the U.S. market.

Chairman TOM DAVIS. OK.

Dr. Gerberding, let me ask you. Getting parochial, Virginia, Maryland, and D.C., this whole region, we are all heavily dependent on Chiron to supply our vaccines for the public sector. How has the CDC worked with Aventis to redistribute the portion of the Aventis flu zone doses to States that contracted solely with Chiron?

Dr. GERBERDING. On October 5th, 33 million doses of Aventis vaccine had already been distributed, but there were a projected 25 million doses left to be allocated. The first phase of allocation was targeted to people who need the vaccine the most. So looking at the Aventis purchasers, as well as the public sector purchases, we did everything we could to ensure that we got all the doses out to the Vaccine for Children Program, doses going to nursing home and to other high-priority obvious areas where there were most likely to be people who needed it.

Once that plan was developed and implemented, then the remaining 12 million or so doses needed to be allocated, and in this step the State health officials stepped in and said we will work with CDC and Aventis to target those doses of vaccine to the places in our communities that need vaccine the most. Thus the States have really done an assessment of where it is needed, how it is needed, and we have made sure it has gotten there.

In this process of working with the States to allocate the vaccine, we have made available to them, for the first time ever, proprietary information on a secure Web base that tells them now just how many doses, but exactly to whom Aventis shipped the doses. The Chiron distributes have been providing that information now as well. Therefore the doses are going, at the direction of the State health officials, to the people in those jurisdictions who need them the most.

Chairman TOM DAVIS. Let me ask. If you go back to October, it looked like we had about 50 million doses nationally available, is that about right?

Dr. GERBERDING. In October we had already used 33 million of the——

Chairman TOM DAVIS. I am talking about total doses available. With Chiron not being able to produce it, we were going to be around 50 million doses. Is that right?

Dr. GERBERDING. A total of 61 million doses total this year, including 3 million doses of the FluMist.

Chairman TOM DAVIS. But part of that is because we have stepped up efforts since October, isn't that correct?

Dr. GERBERDING. Right. Exactly.

Chairman TOM DAVIS. I am just saying it was about——

Dr. GERBERDING. Aventis had a higher than expected yield, and they were also able to get a few million more doses out of the production line.

Chairman TOM DAVIS. So we are up to 61? Will that go any higher, do you think, looking at some of the foreign distribution?

Dr. Crawford, do you know?

Mr. CRAWFORD. Yes.

Chairman TOM DAVIS. We were at 75 million doses last year. What do we expect to be at the end of the flu season? How many doses can we reasonably expect to have on the street, available to the public? Anybody want to take a stab at that?

Mr. CRAWFORD. Yes. We have made contacts with a variety of companies, and we are in final negotiations with three of them that are in other countries, and it is possible that we will have an additional 5 or 6 million doses cleared for shipment to the United States by the first of the year. The exact figure we don't know at this point because we are continuing to negotiate, but we have sent inspectors to those plants and they have filed their findings. And I expect to have on the first plant, which is actually the largest one, a recommendation by the end of this week, and then I can make a determination as to whether or not it meets U.S. standards and can be brought in under special circumstances.

Chairman TOM DAVIS. You would agree, though, we need more suppliers to avert this kind of thing in the future? Does everybody agree with that?

Dr. GERBERDING. Absolutely.

Mr. CRAWFORD. Yes.

Chairman TOM DAVIS. And that means the FDA is going to have to be proactive in going out and getting some of these other areas licensed, is a fair assumption?

Mr. CRAWFORD. It does. Yes.

Chairman TOM DAVIS. Dr. Gerberding, let me just conclude. What lessons from our response to this year's flu vaccine shortage are really relevant to bioterrorism preparedness?

Dr. GERBERDING. Well, the systems that we have been using to track and allocate flu this year are the same systems that we would use for a pandemic or for a terrorism event. I think it has been a challenging exercise. We have been asking a lot of our public health system in this regard, but the laboratory network, the communication network, the emergency operations network, and really the countermeasure allocation system that we have executed are all critical components of any emerging threat, including terrorism.

Chairman TOM DAVIS. And they are working pretty well under these circumstances?

Dr. GERBERDING. Well, so far we have been very pleased with the steps that have been taken and the success that we have had, but, again, it is early in the season and we have a long way to go before we are through with this.

Chairman TOM DAVIS. Thank you very much.

Mr. Waxman, you have 15 minutes.

Mr. WAXMAN. Thank you, Mr. Chairman.

Dr. Crawford, I want to start my questions with you. In 1999 the Food and Drug Administration inspectors went to a Liverpool plant and they identified manufacturing problems—this was before Chiron purchased it—and the inspectors responded to these problems by issuing a warning letter. And as I understand the significance of a warning letter, it is an official enforcement action. If the manufacturer doesn't correct the problems or remedy the violations, FDA can initiate legal action against them. So it is a serious matter. And, in addition, once there is a warning letter, it gen-

erally ensures that another inspection will be conducted to make sure the problems have in fact been fixed. So that is what happened in 1999.

In June 2003 FDA inspectors went out again. There were four inspectors, as I understand it, to look at this Chiron plant in Liverpool. And they found bacterial contamination, in some cases 1,000 times higher than expected. They found unsanitary practices. They found the plant was not doing an adequate job investigating and correcting these problems. The June 2003 inspection team recommended, as I understand it, unanimously that there be an official action, as there was in 1999. Instead of a warning letter being sent, which would be official actions, the recommendation was "downgraded to a request for voluntary action by the company," a request that carries no legal weight and that did not lead to a prompt followup inspection.

What I am concerned about is why did FDA downgrade its response and ask for only a voluntary action?

Mr. CRAWFORD. It is because of the progress that the plant was making. We issued what is called a 483, which is a statement of what we think should be corrected. We stayed in touch with the plant as they moved toward the end of that production cycle. Two things happened: they responded very well, they corrected the problems; and then the vaccine production in that plant for that year, which was ready for our evaluation a few weeks later, turned out to be OK. The 2003 production was not contaminated. So they had in fact completed what we wanted them to do and there was no need to have mandatory or a warning letter.

Mr. WAXMAN. Well, there was no need, but there could have been, and that would have enforced another inspection. In fact, did FDA go back to the plant to inspect whether conditions in the plant were actually improving as you thought they were or you hoped they were? Did you schedule another inspection, as FDA would likely have done if you had taken an official enforcement action?

Mr. CRAWFORD. Well, two things happened, as I mentioned.

Mr. WAXMAN. Well, could you answer yes or no on that question?

Mr. CRAWFORD. Pardon me?

Mr. WAXMAN. Could you answer yes or no?

Mr. CRAWFORD. Would you restate the question?

Mr. WAXMAN. Well, you didn't send an official letter, which would require followup inspection; and you thought things were improving. And I want to know did FDA go back to the plant and inspect whether the conditions in the plant were actually improving, as you hoped they were, and did you schedule another inspection, as FDA would have done had you issued an official letter?

Mr. CRAWFORD. Well, it is not possible to answer that yes or no because we did go back in August 2004. If that is the question, the answer is yes.

Mr. WAXMAN. Well, the answer wouldn't be yes, because under an official letter you would have gone back earlier than that.

Mr. CRAWFORD. But they corrected the problems.

Mr. WAXMAN. Well, how do you know they corrected the problems?

Mr. CRAWFORD. Because we got the vaccine produced and it was OK.

Mr. WAXMAN. That was the final product.

Mr. CRAWFORD. In 2003.

Mr. WAXMAN. But in the 2003 inspection your people said that there were unsanitary conditions there, that there is a high bacterial contamination. Maybe it wasn't in the final product that you saw, but it certainly became the reason why the British shut down the plant in 2004, isn't that correct?

Mr. CRAWFORD. No, that is not correct.

Mr. WAXMAN. It is not correct? OK, we will get to that in a minute.

I think it was a mistake for you not to have gone back earlier than 2004. If you had issued an official letter, you would have had to have gone back earlier. And the reason it was a mistake is conditions weren't getting better, as you thought they were; they were deteriorating. But because you weren't there in the plant until 2004, when we already had a problem that was much worse, you had no idea how bad things actually were. Unfortunately, what happened at the Chiron plant I think is emblematic of larger problems at your agency, but let me get to that in a minute as well.

FDA inspected the flu vaccine supply in June 2003. The report of the inspectors found serious problems in 20 areas of vaccine manufacturing and distributing. You stated that FDA's oversight in 2003 had no relevancy for 2004. I want to ask you first about the finding of high bio burden, meaning high levels of bacteria in the vaccine production process. In 2003 FDA found evidence of bio burden more than 1,000 times higher than expected, even after they had this filtration system to stop it. FDA also found that on repeated occasions the vaccine pools had been contaminated with potentially lethal bacterial called serratia; and FDA even found contamination in the vaccine after sterile filtration, which is supposed to eliminate any potential for bacterial growth.

Now, is it not true that if these findings of high bio burden, how you can say they had no relevancy, the problem that led to the closure of the plant in 2004?

Mr. CRAWFORD. Well, as you mentioned earlier, in 1999 we had this same sort of problem with the bio burden. As you know, every vaccine production lot starts off with a bio burden, and production is in large place decontaminating it so that it goes back to a sterile situation. After 1999 we had a perfectly fine production in 2000; after the findings of 2003, that vaccine turned out to be OK. There was no linkage between it and what happened in 2004.

Mr. WAXMAN. Well, in the documents that we finally got from you—and it took a while to get it—this was the inspection in 2004. They talked about this high bio burden in the lots and they said "not corrected from previous inspections in 2003, in that similar occurrences noted during this inspection." So when they went back in 2004, the FDA inspectors found the same problems they found in 2003, a high level of bacteria that can contaminate the supply. And I think this is a key point. In 2003 FDA found problems at the company investigating sterility failure, and it was the failure at the plant to investigate and correct the 2004 contamination that led to the shutdown.

Mr. CRAWFORD. No, that is not correct.

Mr. WAXMAN. What led to the——

Mr. CRAWFORD. Bio burden is present in every production lot of flu vaccine; it starts with a bio burden and then the point is that the bio burden has to be reduced and eliminated.

Mr. WAXMAN. They had problems with the bio burden; it was 1,000 times more than it was supposed to have been. Is that right?

Mr. CRAWFORD. What year are you talking about?

Mr. WAXMAN. 2003.

Mr. CRAWFORD. They had problems, but they were able to decontaminate it, so the vaccine actually went on the market.

Mr. WAXMAN. Well, your inspectors went back in 2004, and they said the problem had not been corrected for the bio burden. When you finally went back on October 15, 2004, you found a high bio burden that hadn't been adequately investigated. And this inspection expressly stated it wasn't corrected from the previous inspection in 2003. When you read these documents, it is clear that the bio burden problems and Chiron's failure to be able to identify and correct them were a significant factor behind the closure of the facility. They existed in 2003, they weren't corrected; they got worse in 2004. As I mentioned, the FDA inspectors, in 2003, found evidence of contamination in the vaccine, even after sterile filtration that is supposed to remove all bacteria, "a potential source of contamination was identified in the aseptic connections between the tanks of the vaccine and the formulation area."

So in June 2003 FDA found that the company had failed to address these problems with these connectors, and this year Chiron investigated its most recent contamination problems and the company found a major weakness and possible cause of the contamination in the aseptic connections. FDA scientists wrote, "The contamination most likely occurred during the multiple number of aseptic connections in the formulation stage."

So let me ask you this question. Aseptic connections were identified as a potential source of contamination in 2003. They weren't fixed. They then were identified by both Chiron and FDA officials as a likely source of contamination in 2004. Doesn't that make the 2003 inspection and FDA's failure to followup to make sure the problems were fixed relevant to the problems in 2004?

Mr. CRAWFORD. No. The bio burden comes in with the eggs, the chicken eggs that the virus is grown in, and it is discreet to that particular year. The bio burden of 2003 is long gone. So you bring in a new bio burden with the new chicken eggs, and what you have to do is reduce that load through various means.

Mr. WAXMAN. Your staff met with our staff this week, and when they met, your senior FDA officials conceded that a number of findings in 2003 were relevant to the 2004 problems. These included problems not only with the bio burden and the aseptic connections, but also with the basic sanitary practices in the facility. In essence, what they told us is that the problems identified in 2003 didn't get better, as FDA hoped they would; instead, as production volumes increased in 2004, the problems at the plant expanded, ultimately leading to the shut down of the facility.

I would submit that this was a serious cost of the FDA failure to be more vigilant. If the agency had taken official enforcement action, as the FDA inspectors asked for, as they recommended, the problems at the plant might have been corrected and the flu vac-

cine crisis might have been averted. And if FDA would be more honest about what happened and the mistakes that were made, the public would have greater confidence that the agency will correct its mistakes and can be trusted in the future.

Dr. Crawford, I know you want to say this is different, but essentially what we have is a plant that has had troubled sanitary conditions in its production, and those troubled sanitary conditions eventually led to the contamination of the vaccine supply. That is what caused the shutdown by the British. That is what your FDA people saw when they finally got out there. I would submit to you that now that we have these documents, it is not good enough to say, well, things were getting better. They weren't getting better; the problems hadn't been corrected; the production was being increased. And with the increase in production and the facilities not having their sanitary problems corrected, we ended up with a breakdown.

Mr. CRAWFORD. Well, I had to condemn, as you know, the production for this year based on the fact that the bio burden could not be reduced this year; and that didn't happen in 2003. It was one of the toughest decisions I ever had to make, but we could not allow that vaccine into the United States. We had to take that particular step, and we are working now with the British to see what can be done for the next flu season.

Mr. WAXMAN. Well, you say it was a very tough decision for you to make, but in fact it wasn't you that made it, it was the British who shut down the facility and prohibited Chiron from selling any vaccine.

Mr. CRAWFORD. No, we already had between 6 and 7 million doses in the United States. We sent a team over to do an inspection of the plant, and then I had to make the decision. That is the sequence of events.

Mr. WAXMAN. That was after the British action or before the British action?

Mr. CRAWFORD. That was when the British notified that they were suspending the license. We already had the vaccine here in the United States.

Mr. WAXMAN. Well, the point is clear: the British suspended the license because these problems were contaminating the vaccine supply. You had some of the supply here; you decided you can't use that supply. The British had already shut down the plant.

You said that there was no relevancy to the June 2003 inspection to later problems. I just dispute that statement. You said that the FDA assured that Chiron took all steps to resolve the problems from 2003. But FDA had not done any reinspection of the facility, and your own inspectors found this to be untrue in October of this year, finding that a key issue involving contamination was not corrected since the previous inspection.

All of these statements that I think were made by you and others in the administration that were not accurate had the effect of reassuring Americans, before the election, about the Bush administration's role in the flu vaccine shortage. Prior to the election, FDA withheld documents from this committee that revealed the truth. FDA ostensibly said that there was a reason to not send us the documents at the time we requested, because the individuals who

were to produce the documents were too busy trying to find more vaccine. But when we look at the fax cover sheets now with these documents, they were sent to you by individuals on October 18th, 2 days prior to our deadline, just as I had been informed by an FDA employee.

So what I am picking up here is a pattern of misleading statements, and maybe even political calculations, that I think reflect poorly on the administration, but I think they do an enormous amount of damage to the credibility of the FDA.

I did want to get into the other enforcement actions that have not been followed through by FDA. We have seen just dramatic decreases in enforcing the law. I know you consider this a routine procedure, but this is not a routine procedure when you are talking about half the vaccine supply of the United States.

Mr. CRAWFORD. Can I respond to some of this?

Mr. WAXMAN. Please.

Mr. CRAWFORD. Every statement I made was accurate. As you know, the chairman granted us an extension of time so we could produce the documents that were requested all together, and not just dribble them in. So we complied with the chairman's timing.

Mr. WAXMAN. I just want to ask this one last question, because my time has expired. How could you say there was no relevance for the inspection in 2003, when your inspection in 2004 had specifically noted on it by the inspectors that the previous problems had not been corrected from 2003, which have to do with contamination of the facility?

Mr. CRAWFORD. The problems were corrected, because the vaccine production was good and could be used. They use the same terms, and that may be where the confusion is coming in.

Mr. WAXMAN. Your inspectors said that wasn't true, though.

Mr. CRAWFORD. Because if something happened like in 1999——

Mr. WAXMAN. So you think the problem was——

Chairman TOM DAVIS. The gentleman's time has expired.

Mr. Crawford, I want to give you an opportunity, if you want, to finish that.

Mr. CRAWFORD. No, I was just saying they used the same terms of art to describe inspections, you know, maybe over a 20 year period. That doesn't mean that whatever it is, like the bio burden doesn't occur from year to year——

Chairman TOM DAVIS. Well, let me ask. You could have taken the 1999 inspection and said that had a problem with 2004 as well, couldn't you, under the same logic?

Mr. CRAWFORD. Absolutely.

Mr. WAXMAN. Would the gentleman yield just on that point?

We are not talking about something years before, we are talking about 1 year earlier they told you there was a problem. You said it didn't show up, so it was corrected, but it didn't appear to be corrected according to your own inspectors.

Chairman TOM DAVIS. I think he just explained it.

Mr. WAXMAN. If it hadn't been corrected, I think that's a problem——

Mr. CRAWFORD. I have already answered that. They were corrected.

Chairman TOM DAVIS. I think he explained it, and I don't think we are going to reach a closure on this.

Mr. Mica, you are recognized for 5 minutes, and then we will go, Mr. Waxman, to you.

Mr. MICA. Dr. Crawford, don't you realize how many times you deny the accusation, that it is still thrown at you? Dr. Crawford, this little exhibit here, warning letters for biological manufacturing violations have dropped sharply since the fall of 2001. Actually, it goes back to 2000. Are vaccines considered part of biological manufacturing?

Mr. CRAWFORD. Yes, they are.

Mr. MICA. And hasn't there been a significant drop in actual manufacturers of vaccine?

Mr. CRAWFORD. Yes. We are down to only——

Mr. MICA. So if we have fewer people producing the vaccines, then we would have fewer people to go after.

This is a great example of trying to now blame the bureaucrats, as I have said, and FDA. Now, FDA, you don't know it, but you are the fall guy. I have sat on this panel now for 12 years, and I have been through vaccine hearings over that period of time, and first the folks on the other side, they blame the drug manufacturers; these are bad people and they were producing bad stuff, and they were charging too much for it. So then the next routine was it is not just the drug manufacturers, it is those bad insurance companies, because the cost went up dramatically. And I think I cited at the last hearing one vial someone held up and said this only costs $1 or $2, the actual vaccine itself, but the insurance costs $20 or $30, if you could get it.

Now we have no manufacturers in the United States, I guess except for nasal vaccines. We have no insurers, so it is your turn to be the fall guy, and it is your fault. Don't you understand that? Now, you just heard that if you had gotten there a little bit earlier or sent a warning a little bit earlier, there wouldn't be any shortage. Is that correct?

Mr. CRAWFORD. I did hear that.

Mr. MICA. Well, first we go on the premise that you weren't there in time, which you have said you acted in an appropriate manner. But somehow even if you had acted a few weeks earlier, would we have a flu vaccine shortage today?

Mr. CRAWFORD. It wouldn't have had any effect, because it started just in January.

Mr. MICA. And you have made that point. But the root problem and cause, and a lot of folks in Congress don't want to admit it, are, first of all, liability. It is kind of interesting that you had trouble getting to Liverpool to look at a manufacturer.

I submit for the record this article from the International Herald Tribune that shows France, Germany, and Switzerland, for example, followed the so-called British rule, where the losing party pays the cost of winner's lawyer, and it goes on to describe how difficult it is in the countries where they are manufacturing flu vaccine, where you have to fly over and try to find out what they are doing, how much easier it is to produce that and how much more difficult it is to sue and have lawsuits, which have driven manufacturing out of the United States.

Chairman TOM DAVIS. Would the gentleman ask that article be put in the record?

Mr. MICA. Oh, yes. I am sorry.

Chairman TOM DAVIS. Without objection, the article will be entered into the record.

[The information referred to follows:]

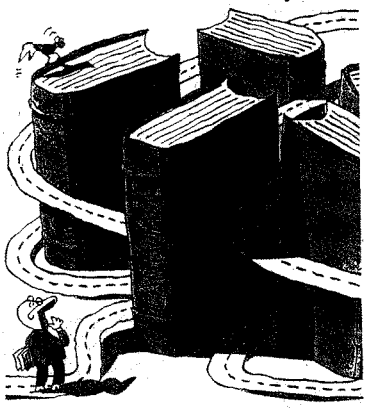
International Herald Tribune
Saturday-Sunday, October 23-24, 2004

atHOM

Legal matters

A wrong move can be costly wh

By Sharon Reier



PARIS

Getting charged with a crime and facing a draconian foreign criminal system may be every expatriate's worst nightmare. But even getting embroiled in a civil suit overseas can prove nasty.

With a different legal system, different attitudes toward litigation and differences in how legal fees are calculated, it is often difficult to know what course of action to take. And making the wrong decision can be costly.

Take the case of Philip Jones, an American banker in London. Jones — who asked that his real name be withheld — was moving from one fashionable London neighborhood to another and placed some furniture in temporary storage. The contract included a fee for insurance to cover damage and loss. But when the movers ruined about $30,000 worth of his belongings and refused to pay or put him in touch with the insurer, Jones refused to pay for storage until they honored his claim.

Jones retained legal counsel with instructions to reach a settlement. But after some time passed, the storage company movers initiated a suit, setting in motion three years of unsuccessful litigation. Five years on, Jones's legal fees have soared to $180,000 for his own lawyers and those of his opponents. And the moving company is charging an additional $54,000 for keeping his belongings in storage for half a decade.

In some countries, potential litigants get clearer guidance than in others as to the potential downside of losing a case. France, Germany and Switzerland, for example, follow the so-called British rule, where the losing party pays the cost of the winner's lawyer as well as his own. In Germany and Switzerland, the fees are quite specific and quite hefty.

"If you have a value in dispute for €2,000, and you lose the case, the litigation risk would be €1,040, including both lawyers and €220 in court costs," said Alexander von Engelhardt, a Berlin lawyer and author of "The Legal Guide to Living in Germany." For a €10,000 case, the loser would pay €3,413. (However, if the opponent wins 80 percent, the loser would pay 80 percent of the winner's legal fee.)

Penalties like these tend to prevent frivolous lawsuits. "The law states we have to frankly tell the probabilities of winning," said von Engelhardt. "But some people don't care too much. They just want a client."

Although the German system tries to encourage rational choice, anger, greed and revenge can get in the way. Some lawyers betray their clients by convincing them they can win a weak case. And some people can decide to sue despite knowing the odds are stacked against them.

Von Engelhardt cited an American lawyer who decided to sue his former girlfriend for money he spent during their few years of cohabitation. He had paid her former debts, financed her child's education and furnished their apartment. "I told him he is not in a very good position," said von Engelhardt. "He said 'I don't care. I want to go forward. There is a point to be made.'"

France and Britain set no limit on lawyer's fees. This means extravagant costs can accumulate over time, and it becomes all the more important to choose an appropriate, trustworthy and competent lawyer.

Most embassies have lists of law firms and lawyers who will handle cases for foreign companies and individuals. But the embassies do not make recommendations.

At the U.S. Embassy in Paris, many firms listed are large international ones that specialize in corporate legal work like mergers and acquisitions or have labor lawyers who protect corporate interests and rarely represent individuals. Others are small U.S. firms and French firms that deal with individual matters from taxation to employment law.

George Bermann, head of European legal studies at Columbia Law School in New York, advised, "Make use of your own network. Find a small, reputable, reasonably priced law firm. And they exist. The lawyer will give you a crude probability of whether you are going to win. He will identify the rule of law that governs your case. He will tell you which court will handle it. As in the United States, it is a question of seeing the facts as they are."

For those with no network, there is always the Internet, the yellow pages or the local bar association.

Look for a lawyer with expertise and success in the area in which you are litigating, whether tenant/landlord, product liability or unfair job dismissal.

Joseph Gourreau, who wrote a treatise about choosing lawyers in Japan, advised colleagues in the legal profession who needed local legal expertise themselves to consult as many of their business and/or legal acquaintances as possible on their experience with a particular law firm, their level of English, their promptness in replying to queries and their ability to achieve practical, cost-effective solutions. The advice is also good for individuals.

At a preliminary consultation, check to see if the lawyer can explain the law clearly. Ask whether the case can be pursued in a cost-effective way. Evaluate how the lawyer's staff treats you, since in all likelihood they will handle some of the work.

While few countries are as litigious as the United States, some countries are becoming more litigious than in the past.

Take France. Michel Puéchavy, a lawyer in Paris, said there are more cases these days because "people are getting more educated so they are more aware of their rights."

Some years ago, he added, if a company had an official building permit, the tenants would think they could be evicted. "But because of the development of communications, of people changing jobs and locations, there is a tendency to have more litigation going to the courts."

But the French system includes both

Finding legal information online

By Meredith Artley

PARIS

The number of lawyers in the world is certainly dwarfed by the number of law-related Web sites. Here a few starting places for legal information online.

Several law sites feature a search engine from Martindale-Hubbell, an information company that provides legal information. Users can search for lawyers and law firms by practice and by area. Martindale-Hubbell has sites in the United States (www.lawyers.com and www.martindale.com), Germany (www.anwalt24.de, in German) and in Israel (www.martindale.co.il). Most of around the world is also available.

The European Law Students' Association has a research tool that can be helpful in providing background on issues and links to publications, such as the British Journal of Criminology and other topic-specific law journals, searchable by country (www.elsa.org/research/lawweb.asp).

If your interests tend toward historical rather than litigious matters, try the "Constitution Finder." This list from the University of Richmond may not have every constitution in the world, but it does have links to the unofficial translation of Qatar's draft constitution and six versions of Poland's constitution. (http://confinder.richmond.edu/)

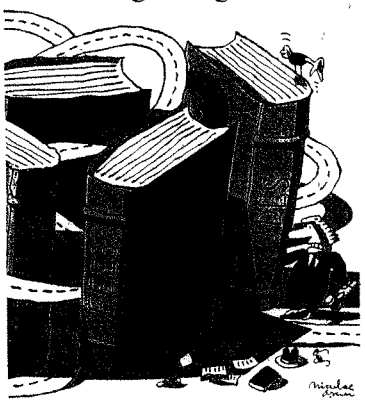
provides links to even more information by country (www.loc.gov/law/guide/nations.html).

More specific searches in Google may help you find Web sites by location. The Law Society of Scotland, for example, has a lawyer directory by practice and region (www.lawscot.org.uk), or try topic-based searches on issues like "Internet law" to find sites like Stanford's Law School's center for Internet and society (http://cyberlaw.stanford.edu).

One piece of advice: use the information you find as general information, not as bona fide legal advice.

Meredith Artley writes the Expat ad-

ıen navigating different systems



Nicolas Asciu/IHT

civil and administrative courts — administrative courts deal with litigation involving the government or branches of the government — which are sometimes in conflict, and can result in a lengthy decision-making process, according to Puéchavy.

He cited an administrative court case involving the city of Nîmes in which the municipal government refused to pay an architect for a year's work on a public building. He eventually won the case but it took so long to settle that the architect was obliged to fire his staff and close his office and he lost his house in bankruptcy. When he went before the European Court of Human Rights in Strasbourg in 1994, it awarded him an additional 640,000 francs, or about €106,600 at the time, due to the unreasonable delay. The entire procedure took 13 years, ending in 1998. (The European Court has also condemned the glacial pace of legal proceedings in many state members of the Council of Europe like Italy, Portugal and Austria.)

Slow and complex litigation typically means high costs. American-style contingency fees, where a lawyer will work on a case for free and participate in the reward, are illegal in France and most Continental countries. Clients should try to get the billing terms in writing in their contract. While some lawyers charge only for letters and complaints and trials, others are beginning to follow the American legal culture and charge for waiting time in court, telephone calls and other services.

Although there is no remedy for the aggravation that litigation entails, there are some remedies for the cost. Legal protection insurance, also known as legal expense insurance, is available in many European countries, with policies covering employment, family, property and motor problems.

At Europe's largest legal expense insurer, DAS in Germany, Peter Stockl, a department head, said the insurance covers up to €300,000 in legal costs, and clients can choose their own lawyers in most countries. Premiums in Germany run around €150 per category. Property is lower.

However, legal expense insurance will not cover every suit. "We only cover ones that have a reasonable prospect of success," said Stockl. For those with a strong case who lose due to poor legal service? "If you have legal insurance, you can also sue your lawyer," he added.

Sharon Rever is a freelance journalist based in Paris.

Mr. MICA. So, one, we need liability and tort reform. Until we get that, folks, you are not going to have health care cost reduced. It is interesting. Pick up the papers today and see how, in a couple of the papers, how many more doctors are closing down their operations, how many health care providers are going out of business or relocating their activities. And that will continue until you get some tort and liability reform in medicine.

Regulatory reform, and it now takes some 8 months, and you have described the process.

Let me go back first. The accusation is maybe we haven't spent enough money, because you have to always spend a lot of money.

NIH, that is Dr. Fauci. In 2001, on research, we had a 10 percent increase from 2001 to 2002. I am not very good at math, but that is what it looks like. Even before all this came out, I don't want to say we doubled, we went from 22.8 to 57.4, which I would say is about 160 percent increase in research. So that goes out the window.

Chairman TOM DAVIS. Does the gentleman have a question? His time has expired.

Mr. MICA. OK.

Chairman TOM DAVIS. Mr. Waxman, you are recognized.

Mr. MICA. Well, I have a number of points and a number of questions. I am willing to stay for a second round, but I am trying to get at the root problem and identify liability, regulatory reform, and I have a host of questions about the States buying this, about guaranteed purchases by the government that have driven up costs. And I will get to those when I have adequate time. Thank you.

Chairman TOM DAVIS. Thank you.

Mr. Waxman, you are recognized for 5 minutes.

Mr. WAXMAN. Mr. Chairman, my colleague, Mr. Mica, didn't get to his questions because he was making absolutely incorrect statements about a lot of different things. He used the opportunity to say we have all, on this side of the isle, accused the manufacturers of being bad people. We have never said that. He is saying it is terrible we are accusing the FDA bureaucrats of maybe not doing the right thing. He doesn't believe that. He thinks it is malpractice or liability issues that has caused the problem we face today.

Well, I would submit that it was not the liability laws that caused the contamination of vaccine in Liverpool. It was the fact that they had unsanitary conditions there. And the inspectors from Britain found that out to be the case, and eventually our own FDA came to conclude that was the case. And I don't consider Dr. Crawford or the FDA to be bad people, but my criticism is that the FDA didn't do enough to stay on top of this issue. They knew from previous inspections in the year before, 2003, that there were problems at that plant, and they never went back for another inspection, until after the British closed the plant down.

I disagree with Dr. Crawford's statement that it was irrelevant that they found that there was contamination in 2003. He said there was contamination in 2003, but that wasn't the problem in 2004. His inspectors said that was the problem in 2004 because it hadn't been corrected in 2003. Well, if you take Dr. Crawford's

statement, it would have to be they corrected it and then they went back into a contaminated state. That doesn't follow.

Now, let me just address the liability issue, because that is really a red herring. The gentleman speaks with a great deal of ignorance, because in the liability area vaccines were a problem; manufacturers weren't making any vaccines for fear of liability. And I authored, and the Congress passed, the vaccine compensation system. It has been very successful by providing a fund to compensate those people who are injured from a vaccination. It has been very successful in keeping people from going to the courts.

The flu vaccine is part of that vaccination system. None of the drug companies, none of the advisory committees to the FDA have come in and said we ought to change the immunization problem, liability for immunization, because it is not a problem in this case. I will leave to another time to discuss the problems of medical malpractice, which I do think is a serious problem causing higher prices in the practice of medicine.

I just think it is important, especially if this is on C–SPAN—I don't know if it is or not, but following his statements made with such abandon and such ignorance, I think somebody should correct the record.

I do want to take advantage of the fact that I have my 5 minutes, and I thank my colleagues for indulging me to do this. But FDA has, I think, undergone a very serious change in direction in the way they have been responding to a number of the problems not just in this area, but this area is emblematic of it.

Well, we have a chart over there, it is the "Warning Letters for Biological Manufacturing Violations." They have dropped sharply since the fall of 2001. You can see in 1997 there were 17; in 1998, 19; and then after 2001 there was 1, 2, and 1. A big drop. We have seen the warning letters to manufacturers who are making false and misleading statements in their advertising. They have dropped dramatically. I would submit that FDA is just not enforcing the law. I was concerned that they just didn't even enforce the food labeling laws, which I also had a part in authoring.

Dr. Crawford, why do you think that is happening at FDA? Why is there a precipitous drop of enforcement actions?

Mr. CRAWFORD. Well, there are not as many people to regulate, not as many companies, as was stated earlier. But we have not lessened our profile in terms of evaluating these companies. But there is variability. If you take it back a long period of time, you will see that some years it is up, some years it is down.

Mr. WAXMAN. Well, we see a dramatic——

Mr. CRAWFORD. But if we still had 20 manufacturers, it would be up higher.

Mr. WAXMAN. Well, I am not talking about just vaccines. But even for the false and misleading statement by all pharmaceutical companies in their advertising, an 80 percent drop in any kind of enforcement actions to be sure the public is not mislead.

Mr. CRAWFORD. Well, we do have fewer drugs that are on the market that have prescription status and are still in patent, also, so that would account for it. But we have not lessened our attention to this kind of activity.

Chairman TOM DAVIS. Thank you.

The gentleman's time has expired.

Mr. Deal, you are recognized for 5 minutes.

Mr. DEAL. Thank you, Mr. Chairman.

Dr. Gerberding, thank you for being here. We appreciate the fact that you and the CDC in my State of Georgia are doing such a good job.

I would like to ask you just briefly you have outlined what you have done in this rather critical situation of a shortage of the flu vaccine in terms of trying to make sure that what is available is delivered to the most critical places. What role, if any, would the CDC play in a normal situation? Do you participate in those decisions in the absence of a shortage?

Dr. GERBERDING. Unlike childhood vaccines, the flu vaccine market is almost entirely in the private sector, so CDC only purchases a very small amount of the vaccine. Therefore, we have only a limited capacity to target or direct our supply to the appropriate individuals. In the last 5 years of vaccine production, every year vaccine doses have gone unused. So, in general, the private sector distribution has targeted to the people who are willing to take vaccine. This year, of course, we are expecting the profile to be very different.

What we do is work with our expert advisory committee, the ACIP, to make the recommendations, the science-based recommendations about who will benefit from vaccine and how they should be vaccinated and when they should be vaccinated; and then the adult immunization mechanisms in the health care delivery system and in the public sector at the State and local level kick in to actually administer it.

This is one of the things that we are looking at, is opportunities to improve our typical coverage of this vaccine, which has never been ideal. We would like to have a higher demand for flu vaccine and we would like to assure that everybody who needs a dose gets it.

Mr. DEAL. You mentioned something about the fact that it is fragile. What is the shelf life of the injectable vaccine? I assume it can't be frozen and preserved in that fashion. What is the shelf life for a vaccine?

Dr. GERBERDING. With this particular vaccine, the shelf life, assuming that the cold storage is maintained properly, is not very relevant because the virus changes every year. So the shelf life is longer than a year, but it doesn't help us very much because we need to make a brand new vaccine every single year; and that is part of the challenge that this particular infectious disease presents to us. That is part of why Dr. Fauci's comments about the need for modernizing the vaccine is so very critical. Imagine if we didn't have to get a flu shot every year. We would be in a very different situation than we are right now.

Mr. DEAL. There are obviously disagreements and opinions as to why we have so few manufacturers. Am I correct that one of the earlier statements, that there is no domestic U.S. manufacturer of an injectable vaccine for the flu? Is that correct, there is no American domestic producer?

Dr. GERBERDING. Aventis is producing vaccine in America, but their headquarters are in France. So the actual manufacturing does occur in the United States for the product that we are using.

Mr. DEAL. How long have we been in a situation of having only two major suppliers? How many years has that situation existed?

Dr. GERBERDING. Ten years ago we had five suppliers, and there has been a gradual attrition over that period of time until just the two injectable suppliers this year.

Mr. DEAL. You know, you would think normally the old adage of supply and demand would work in this environment. Obviously, the normal forces are not at work here. And I would assume that there are some truths to the allegations that the issues of liability play a factor in the fact that we have so few manufacturers available.

Is it simply not a profitable business? And perhaps the second panel is more appropriate, perhaps, to ask that, and we will try to ask it there. But from your perspective, is it the lack of profitability that is limiting the supply?

Dr. GERBERDING. We have a few big problems. One is that we don't have a guaranteed market for the vaccine, and we have unpredictable demand. The second is the manufacturers need a fair price for the product that they are manufacturing; they need to have a business case. The third issue is that making this vaccine is risky, as Chiron discovered this year. This is a very difficult manufacturing process; you start out with a bio burden, and by the end you are supposed to end up with a product that is sterile enough for use, and it is fraught with opportunities for things to go wrong. While liability has played a role, this is the first year that we have recommended flu vaccine for children, which makes it eligible for the vaccine injury compensation program. In past years, because we hadn't recommended it for children, it was not on the list for liability protection. And even that doesn't completely remove all of the concerns about liability, it only covers the things that are in the table.

So it is a complicated set of problems, and the bottom line is the manufacturers need to know that they can make a strong business case for producing this vaccine.

Mr. DEAL. Thank you, Mr. Chairman.

Chairman TOM DAVIS. The gentleman's time has expired. Thank you.

Mr. Van Hollen, you are recognized for 5 minutes.

Mr. VAN HOLLEN. Thank you, Mr. Chairman, and thank you for holding another hearing on this important issue. I want to thank all the witnesses as well.

My first question is obviously this year we have to make the best of the situation that we have before us, and we have to relocate the existing vaccine to those people who are most vulnerable. My question is what is the administration's plan, if any, to prevent this kind of shortage from happening next year and into the future? That is one question.

The second set of questions relates to the issues that Dr. Fauci mentioned, with respect to the avian flu and the pandemic, which is something obviously we need to be preparing ourselves for not just as a Nation, but as an international community. And my ques-

tions there are, No. 1, to what extent do we have cooperation from many of the Asian countries, where this flu is originating, that allows us to detect it early enough to prevent it from spiraling out of control, to the point where we can't isolate it and it becomes a pandemic? And what recommendations, if any, do you have to make sure that we have an early warning system in place, on the ground? I know a number of people at CDC have been working on this and have been frustrated by their lack, for example, of cooperation from the Chinese. So that is one set of issues, the early detection.

The second set of issues relate to a vaccine, and whether or not we are moving ahead as quickly as possible in coming up with a vaccine; whether mutations in the avian influenza would defeat the work that we are doing; and even assuming that we are on the right track with respect to manufacturing a vaccine, what are we doing in terms of the production capability, because we haven't prepared adequately to have a supply of flu vaccine where we know we have certain strains of flu, and at what time would we be prepared from the vaccine production point of view to confront an avian influenza pandemic?

I know that is a lot of questions, but these are obviously big issues.

Dr. GERBERDING. I will start, and then we will start the baton down the table.

In terms of the scenario planning, worst case scenario planning for next year, our Team B is working on this from a CDC perspective, and the Secretary has also called a special task force at the Department to really dig in to what can we do now and what can we do soon to obviate this situation.

One major thing is to work with the existing manufacturers to see what can be done to support the largest possible production. And Dr. Crawford has already mentioned that Aventis and MedImmune are looking at ways that they can increase their production next year. Getting Chiron back online is clearly a high priority for everyone. We may have vaccine available from international manufacturers on an IND, an investigational drug status, and that can allow us to get more doses in, and we are working out the mechanisms for that as we speak. And also we will certainly focus on prioritization early in the season and make sure that we get the targeting when the first dose of vaccine is available, not waiting until more than half of it has been distributed, as we did this year.

So there are some short-term things we can do, but we really look forward to working with the administration and with Congress to figure out if there are additional incentives to help expand the market and get the production up to where we need it to be.

Dr. FAUCI. Let me just extend that, Mr. Van Hollen, and talk about what we are actually doing right now in preparation for pandemic flu; and I alluded to it in my opening statement, but let me just summarize it briefly for you.

We know now that there are a couple of circulating avian influenza viruses. The one that is causing us the most concern is H5N1. Another is H9N2, H7N7, a few others over the years. But let us just focus, for the purpose of an example, on H5N1. What we are

doing now is we are assuming—and it may not be correct, but the assumption I think is an appropriate thing to do, because it will set into motion the machinery that will prepare us if we have to switch in midstream. So we are assuming that the H5N1 is something that we need to worry about, so we are developing two things in parallel. The first are pilot lots. We have isolated it by that rapid method of reverse genetics, and we are in the process of making pilot lots in small amounts, 8,000 to 10,000, from two companies; and we are doing that in order to put them into the clinical trial to determine things: one, is it safe, because we have not vaccinated people with H5N1; we assume it will be because the methodologies essentially stay the same; and, second, how much do you need to inject to get an adequate immune response, is it going to be one dose, two doses, or more?

In parallel, in the assumption that we will have an H5N1 problem, we have contracted with Aventis-Pasteur to get us 2 million commercial lot doses; and that is critically important because the process that gets you the 8,000 to 10,000 doses is not something that you can scale up to 10, 20, 30, 40 million, but the 2 million of the commercial lot doses will set the process in motion that if indeed we do need to scale up, it is much easier to scale up.

Now, on the scenario that perhaps the virus will change so much that the vaccine that we are making is not specifically going to target that virus that now is spreading efficiently human-to-human, the very process of scaling up with an avian virus vaccine is going to put us in good stead to go and meet that challenge.

So we are already doing it now.

Mr. SHAYS [presiding]. The gentleman's time has expired.

Your mic is not on.

Mr. VAN HOLLEN. The issue of international cooperation. I know it was a big question and a lot to cover.

Mr. SHAYS. If there could be a quick answer, I would be happy to entertain it, but not a long one.

Dr. GERBERDING. I can give you a quick answer.

We have a system called the global detection network, and we are investing in laboratories around the world and scaling up our ability to get those isolates and get them to CDC for sequencing and onto the seed vaccine development process. We are also sequencing all strains that are coming in.

Mr. SHAYS. Technically, I am next in line, but I notice we have a number of colleagues in the democratic side of the isle, so I will defer my questions and go to you, Ms. Norton. I think you are next.

Ms. NORTON. Thank you very much, Mr. Shays.

Two questions. One has to do with the kinds of issues local jurisdictions are going through now to think of what they can do now. I asked the District of Columbia Department of Public Health to use its authority to issue its own regulations in an effort to avoid panic and because, as you know, most of the vaccine is in private hands and does not go to public health authorities. They did so. As you know, every State in the United States—this would also be the case in most cities—has the authority, that you apparently don't have, to proceed on its own to avoid a public health crisis. I want to know if you have asked public health authorities to use their own local authority to issue such regulations as they deem suitable,

to advise them that would be an appropriate thing to do in light of what you know about our supply and the delays that are already being experienced by local jurisdictions getting whatever supply is available.

Have you asked those who do have authority to use their authority? For example, a private physician who has regular patients may well be under some very special pressure to give the vaccine to people who are not in high-priority groups. It would be much easier for that physician to say regulations indicate I can't do it then to say that the CDC, who has no authority over me, said I can't do it. So I want to know, since you didn't have the authority, since you left us all out here, whether you have at least asked local public health authorities who do have the authority to use their authority.

Dr. GERBERDING. We have indeed recognized the statutory authority of the State health officers, as well as the local health officials, to make decisions to protect the health of people in their jurisdiction, and that is exactly why we have been able to provide them with the detailed information about their high-risk populations and the vaccines that are there.

Ms. NORTON. I am sorry, I didn't get the answer to my question. Has the CDC specifically advised local authorities that it might be beneficial—not saying that you should do it, but that it might be beneficial—for them to use their own local authority to handle this public health crisis?

Dr. GERBERDING. Yes.

Ms. NORTON. Would you indicate to me whether that has been in a written directive? Could I get a copy of it? How was that advice given? What have you advised them to do specifically?

Dr. GERBERDING. The State health officials have worked with CDC to develop the criteria for vaccine allocation; they are receiving the——

Ms. NORTON. See, you are not answering my question, and I have another question.

Dr. GERBERDING. I am sorry.

Ms. NORTON. I know you have been working with them to develop the criteria. I have asked you something else; it has to do with their legal authority to issue their own regulations so that people know that you are not supposed to give these doses outside of the priority groups. Now, I am not talking about developing and whatever, I am saying very directly have you said you have authority? We are not sure what you would want to do with that authority, but when you have a public health crisis, you should at least consider using that authority if you think that authority would help alleviate the crisis. I have given you the kind of circumstance I am talking about, and I am asking a direct question and I want a yes or no answer.

Dr. GERBERDING. Yes.

Ms. NORTON. Or if not a no—and if a yes answer, then my follow-up question was what did you say? Give me a copy of it. I don't know that my authority has received anything; at least they have not reported any such thing to me.

Dr. GERBERDING. We would be happy to provide you that information.

Ms. NORTON. Well, what did you say? I am asking you a question here.

Dr. GERBERDING. We said we encourage you to exercise your statutory authority to make decisions about vaccine allocation for your district. And we have also provided them with information from our public health law program, which gives them the legal guidance from the statutes that are applicable to them.

Ms. NORTON. Well, that is certainly at variance with what I was told. Therefore, I am asking, by the end of the day, would you provide me with a copy of that? We were told that you all did not consider it appropriate to do so. And I am very pleased if you have reconsidered.

Dr. GERBERDING. We consider it appropriate for them to use their authorities as they see fit.

Ms. NORTON. Well, obviously as they see fit. I am not asking you to demand what you can't demand. I would like to have a copy before the end of the day so I can make sure my own public health authority knows that has been your recommendation.

Mr. SHAYS. Time has expired and we need to move.

Between Mrs. Maloney and Mr. Sanders, have you worked out who goes next?

Mr. SANDERS. She won.

Mr. SHAYS. OK.

Mrs. Maloney, you are next.

Mrs. MALONEY. Thank you.

First of all, I would like to thank the witnesses for your testimony.

Just to underscore how critical this challenge is, two flu outbreaks in New York City alone have led to the death of four people and 13 hospitalizations in the past few weeks. Our mayor—and I congratulate him for this action—has reached out to purchase, along with New Mexico and Illinois, 200,000 doses of flu vaccine from European suppliers. And while this is not enough to cover everyone in New York City, it would cover our high-risk residents and it would supply roughly 570,000 doses of vaccine.

I wrote a letter, along with other members of the New York delegation, in a bipartisan way, to Commissioner Crawford, asking FDA to expedite the process for the review for these doses, and I really want to know where that is. We need to get this vaccine. We have wholesalers that are available in Europe that will sell to us. How soon can we get it approved?

Mr. CRAWFORD. We are going through a process which involves, first of all, getting the lot numbers of the vaccine, which the Governors and the mayor have kindly provided. The company that manufactures the vaccine has authenticated those lot numbers, they are in fact legitimate production from their facilities. And what we are now doing is getting what is called the pedigree, and that is where the vaccine has been, where it has been shipped to and whether or not it has been kept refrigerated. We should have all that information in the next few days and we should be able to make a determination of whether or not it is suitable very shortly after that. I can't give you a specific date, but we have up to 750,000 doses nationwide that we are dealing with, including the

200,000 for New York City, and we should be able to do all of them at the same time.

Mrs. MALONEY. I would like to ask CDC what the justification is that you have for not buying the many doses of vaccine that is available from wholesalers in Europe right now? That vaccine is available, unlike the vaccine from manufacturers which may not be available until January, which may be too late for many high-risk patients.

Dr. GERBERDING. I think the answer is the same as the answer that Dr. Crawford provided. We can't purchase vaccine until it has been verified that it meets the importation criteria and has been handled in a way. The vaccine in question has already left the manufacturer, so it is out in the wholesale arena, and we are not allowed to purchase that until we know that it has been properly stored and maintained, and that its safety can be guaranteed.

Mrs. MALONEY. So you are reviewing wholesale production and sale at this point, CDC?

Dr. GERBERDING. We are working with FDA to do everything we can to get international vaccine sources into this country safely and quickly.

Mrs. MALONEY. I would like to go back to the timing of the review. The Wall Street Journal this week quoted John Taylor, FDA's Associate Commissioner for Regulatory Affairs, and he said that in 2003 FDA's Liverpool inspection showed systemic quality control issues at the Chiron facility. And yet, even though FDA knew that they had these problems, you never returned to the plant to verify that things had been rectified and that the vaccine would meet minimum safety standards, and you relied on Chiron's assurances that they had corrected it. And even after Chiron announced on August 27th that it had identified contamination in some of the flu vaccine, you still did not schedule an inspection.

So my question is if FDA had responded quickly to the August 27th announcement, could we have avoided the severity of the problem, if you had gone in there early and worked with them and corrected it, instead of waiting? And then, second, if you had alerted Aventis, the second company that is verified to produce the vaccine, of the problem, could FDA have redirected their vaccine to the high-risk individuals? By the time the announcement came to Aventis that we had a challenge and that there was a shortage, they had already shipped almost 60 percent of the vaccine; but it had not been shipped before August 27th.

So, in short, I think that the American people deserve more from FDA in their management in a proactive way of making sure that the vaccine was there and checking on it in advance. But from this timetable that we have, you didn't even go for an inspection, you didn't followup, you didn't alert Aventis. And then there comes another question: Why do we only have two companies with this vaccine? I shudder to think if it had been small pox vaccine and we had a breakout of some terrible disease.

Chairman TOM DAVIS [presiding]. The gentlelady's time has expired.

Dr. Crawford.

Mr. CRAWFORD. Actually, we don't control how many companies want to enter the U.S. market. There is not much we can do about that. We wish we had the 20 manufacturers we formerly did.

We did followup on what we found in 2003, and, actually, the vaccine for that year, which was the subject of that inspection, turned out to be OK, and it was used. Then a new batch of vaccine was prepared for this year, during this year. It was too late in August for them to start over again, because it takes from roughly January or February until it finally comes offline for it to be produced. But we have, once we got the information, gone to other manufacturers, and we have been able to find millions of more doses, and we are still looking with the cooperation of Governors in States and elsewhere to complete as large a quantity of vaccine as we possibly can.

Chairman TOM DAVIS. OK, Mr. Sanders, you are recognized for 5 minutes.

Mr. SANDERS. Thank you very much. Mr. Chairman, the issue that I want to pursue is a very simple one, and that is the Federal Government and numerous States, including the State of Vermont—Dr. Crawford, you and I chatted about this very briefly, and I discussed it with Secretary Thompson as well very briefly.

Mr. CRAWFORD. Yes.

Mr. SANDERS. The Feds and the States have identified over 5 million flu vaccine doses that are available in Canada and in Europe. And we are not talking about obviously fly by-night companies, we are talking about Aventis, we are talking about Glaxo, we are talking about ID Biomedical in Canada. And to the best of my knowledge, these flu vaccines have already been used and distributed in Europe and in Canada, like a new product.

My question is, given the crisis that we face—Mrs. Maloney mentioned that people in New York are already dying; the fear is that there could be a serious outbreak of flu—why does it take so long? I mean, you have reputable companies in countries which are well regulated, Europe and Canada. You have a product which has already been distributed to the people in those countries. Why, last month, did you not send a host of inspectors there to make the check of the plan, of the dosages, and get them out to the people? Dr. Crawford.

Mr. CRAWFORD. It won't take very much longer. The process is basically threefold. These vaccines, although used in other countries, are not approved for use in the United States, so we have to speed up that process. The way we do it is we contacted these three manufacturers, got their production records, and also what is called their master file of how they produce the vaccine.

Mr. SANDERS. That is the first day. What did you do on the second day?

Mr. CRAWFORD. The second thing is we sent inspectors, and they have now all completed their inspection of these facilities. They will file their reports with me. The first one——

Mr. SANDERS. I don't mean to be rude. We don't have a lot of time. I understand all that. That is legitimate. That is 2 days' worth of work. Why has it taken it a month?

Mr. CRAWFORD. No, it is about a month worth of work.

Mr. SANDERS. Why?

Mr. CRAWFORD. Because you have to get these master files. First you have to get the cooperation.

Mr. SANDERS. Yeah, we have things like email; you have planes to get you over there.

Mr. CRAWFORD. No, no, no. Let me explain. You have to get the cooperation of the company; they have first got to decide that they want to give it to us. That took a lot of stuff.

Mr. SANDERS. We have talked in Vermont to some of these companies; they want to sell their product. You are not giving me a good—briefly, why does it take——

Mr. CRAWFORD. And then, finally, we have to give them approval to bring it in under what is called an investigational new drug application.

Mr. SANDERS. All right, I will give you 3 days. This does not take a month. You have people in my State who are very concerned. All over this country they are concerned.

Mr. CRAWFORD. I can assure you we will get it as quickly as we possibly can.

Mr. SANDERS. But you see, I want to raise a question, and tell me that maybe I am being overly concerned here. Some of us, including the majority in the House, believe in prescription drug re-importation. We think that it is insane that Americans have to pay two, three, five times more for the same product that our friends in Canada and Europe do. If we had prescription drug re-importation, those products would be in this country a month ago. I hope very much that, given the administration's opposition to re-importation, you are not making this more difficult than it should be. Could you comment on that?

Mr. CRAWFORD. If the question is are we making it more difficult than it should be, the answer is no.

Mr. SANDERS. But you still haven't given me a reason why, with all of the resources at the FDA's command, why we have not approved those medicines and why we have not distributed them.

Mr. CRAWFORD. Well, I told you we are doing it as quickly as we can, and that it is a matter of days away before we make a determination about these particular products.

Mr. SANDERS. Then how long does it take you to make a determination?

Mr. CRAWFORD. Well, it depends on what the data is we get, how we evaluate it, whether or not we can——

Mr. SANDERS. All right, explain to the people who are watching this. You have a product that has been widely distributed in Europe and Canada; you are inspecting these facilities of major drug companies, above-board, reputable. How long is the determination going to take and why is there so much question?

Mr. CRAWFORD. It is variable. It is normally about a month's time before we reach an evaluation, because we have to get all the records, we have to visit the plant, we have to make a determination. We have to be sure that the vaccine brought in won't injure the American people.

Mr. SANDERS. Well, of course.

Mr. CRAWFORD. By law, it has to be done on an investigational new drug application, and that is the way it is.

Mr. SANDERS. How long is this determination process going to take?

Mr. CRAWFORD. It is just about over.

Mr. SANDERS. So you think you can make a decision within a week?

Mr. CRAWFORD. I wouldn't be held to a week, but I think it could be quicker than that in one case.

Mr. SANDERS. All right, now, my question is—and I know you and I chatted about this——

Chairman TOM DAVIS. The gentleman's time has expired.

Mr. SANDERS. Thirty seconds.

Chairman TOM DAVIS. If he can state his question quickly.

Mr. SANDERS. Thirty seconds.

Chairman TOM DAVIS. State the question.

Mr. SANDERS. All right.

Are you going to allow States and cities to go forward or are these European and Canadian drugs going to come into the United States and you guys will distribute it?

Mr. CRAWFORD. We have been working with the States. Some of them want to bring them in directly, and they already have made contacts and so forth, so we will work with them on an individual case-by-case basis.

Mr. SANDERS. Thank you very much.

Chairman TOM DAVIS. If I could just followup. I think you testified earlier you believe that some of these drugs from foreign manufacturers are going to be certified and be able to come in the country.

Mr. CRAWFORD. Some of these vaccines, yes.

Chairman TOM DAVIS. Vaccines, right. Thank you very much.

Who is next over here? Mr. Tierney, have you asked questions yet? I think you were here. Would you like 5 minutes? We still have a couple questioners here.

Mr. TIERNEY. Thank you, Mr. Chairman.

Dr. Crawford, let me ask you a set of questions here about Chiron's plant in Liverpool, England. It was subject to an inspection both by the FDA and by the British counterpart, the MHRA. Now, you have repeatedly stated that both agencies responded to the August 2004 reports of contamination in a similar fashion. I think at the committee's October 8th hearing you said that both FDA and the MHRA performed inspections that were about the same thing. In a later press conference with Secretary Thompson, you stated, "We would have, 5 hours later, made the same conclusions as the British; we were in synchrony with them."

So I want to just ask about some of the differences between the British and the U.S. approach to that August Chiron announcement of contamination. When the initial contamination was reported, it was the United States, and not the U.K., that immediately lost several million doses. It was the United States, and not the U.K., that was depending on Chiron for about half of its vaccine supply. Yet, it was the British, who had, I think, much less at stake with this vaccine facility than the United States, that sent an inspection team to the facility within a few weeks of the August 25 announcement, and the British who also sent a second inspection team to the plant at the end of September. Why didn't our

FDA respond forcefully to the August contamination by sending inspectors to the plant, as did the British?

Mr. CRAWFORD. We had inspectors in the plant on August 25, and——

Mr. TIERNEY. But if I could just interrupt for a minute. You had somebody there by coincidence, who was inspecting an entirely separate and discreet issue?

Mr. CRAWFORD. Yes. They were getting up a different line. But they were there and they were alerted by Chiron. They went over some records and made some recommendations. Subsequent to that, we, along with the CDC arranged for a series of calls, at least once a week, to find out how they were doing with their bio burden in that plant. Things appeared to be going well up until the final reports, which came to the British and also came to us in virtually the same amount of time. They scheduled an inspection, as did we.

Mr. TIERNEY. But your inspectors over there did not do the same kind of thorough inspection that the British team did when it went in.

Mr. CRAWFORD. I can't speak for the British.

Mr. TIERNEY. Well, you can speak for yours, and you know that they did a more thorough examination. Your person did a somewhat cursory look at some records, but didn't actually have a full-blown inspection that you ordinarily would have had in response to this type of an emergency.

Mr. CRAWFORD. Well, we would have come to the same conclusion based on our lot release program; we would not have allowed the product into circulation. And I made that decision following an inspection that took place onsite.

Mr. TIERNEY. Let me look at another point of difference on this. The British received a draft of the Chiron inspection sometime in mid-September, before even their second inspection. Yet, on the other hand, we never received the report until the British actually shut down the facility, sometime in October. How do you explain that the British got that inspection report so much more quickly than the FDA did?

Mr. CRAWFORD. We were getting a weekly update from the company, and we were scheduled for the final report on October 5. The Chiron facility was under instruction from the U.S. Government to quarantine the product, which they did, so none of it could be released, starting on August 25. So I believe we had control. In fact, we did have control, because none of it got out.

Mr. TIERNEY. But there was a serious gap, and the British seemed to be on top of this thing. They are getting a report before their second inspection; we get it weeks later. I mean, it would seem to me like they were a lot more aggressive, even though they had less at stake than we did, and I am wondering why it was.

Mr. CRAWFORD. Well, we got a report every week, but the final report was scheduled for October 5 for both governments, because that was the end of the run. You can't get a final report until they finish.

Mr. TIERNEY. Well, is it fair to say, though, that the FDA was caught a little flat-footed about the British closing of that plant, that the FDA didn't even know it was going to happen until after the fact?

Mr. CRAWFORD. Well, by law, they could not communicate with us, and we did not know that they were going to do that on October 5, no, that is correct.

Mr. TIERNEY. The law that you are mentioning is a British law, right?

Mr. CRAWFORD. It is.

Mr. TIERNEY. But that can be waived. We know that because it was waived after the fact.

Mr. CRAWFORD. Well, the British issued a press statement about 3 days after the October 5 determination, in which they said they were constrained by their law from communicating to us or the other 98 countries.

Mr. TIERNEY. But it could be waived, and it was waived after the fact.

Mr. CRAWFORD. Well, now we are able to work together because of the company's willingness to share it.

Mr. TIERNEY. So my question, I guess, is this. It is a very important source of supply for us.

Mr. CRAWFORD. Yes.

Mr. TIERNEY. We had a lot at stake. Why would we rely simply on the company's analysis or report of facts, or whatever? Why hadn't we asked for a waiver from the company, which tells us now that they would have certainly cooperated? Why didn't we ask for information from more than one source as this thing was developing? Why not say to the company ahead of time we need a waiver; we want to not only find out from you what is going on, we want to talk to our British counterparts and we want to have our own inspections, we want to stay on top of this thing because we have so much at stake?

Mr. CRAWFORD. We were getting all the information we were asking for; there was no need to do that.

Chairman TOM DAVIS. I thank the gentleman.

At this time, Mr. Cummings, you have 5 minutes.

Mr. CUMMINGS. Thank you very much, Mr. Chairman. I really appreciate it.

Let me just ask you this. I just want to make sure we are clear. Did FDA make any mistakes?

Mr. CRAWFORD. FDA is not perfect. We followed our situation here as we traditionally do, and at the end of the time we got the final report on schedule, October 5. We sent an inspection team over, and then we had to make the determination that this vaccine was not usable; therefore, it never got the U.S. population.

Mr. CUMMINGS. So you are saying that made——

Mr. CRAWFORD. So, therefore, it was a success.

Mr. CUMMINGS. Whoa, whoa, whoa. Excuse me. Are you telling us that FDA made no mistakes?

Mr. CRAWFORD. In this vaccine thing?

Mr. CUMMINGS. Yes.

Mr. CRAWFORD. No. It never got on the market.

Mr. CUMMINGS. I can't hear you.

Mr. CRAWFORD. It never got on the market.

Mr. CUMMINGS. FDA rejected the recommendations of the inspectors and decided not to pursue official enforcement action against Chiron in June 2003. As a result, the problems at the facility were

not public, and told investors that the inspection showed the plant was really "in very good shape." Was that a mistake?

Mr. CRAWFORD. On the 2003 vaccine production, we asked them to make some corrections; they did. That vaccine was fine.

Mr. CUMMINGS. So you are saying you didn't make a mistake there.

Mr. CRAWFORD. No, because the vaccine was fine.

Mr. CUMMINGS. FDA failed to reinspect the facility to find out if any of the problems were corrected or the company's plan was being implemented as proposed. Yes or no, was that a mistake?

Mr. CRAWFORD. We reinspected by taking information from them all along, so, no, we did not violate our procedures.

Mr. CUMMINGS. So again you didn't make a mistake.

FDA declined to meet with Chiron after it requested a meeting "as soon as possible" to discuss plans to respond to the June 2003 inspection. This meeting could have helped the company understand the severity of the problems. Was that a mistake?

Mr. CRAWFORD. We met with Chiron.

Mr. CUMMINGS. FDA delayed sending a copy of the full inspection report to Chiron by 9 months, from September 2003 to June 2004. By the time the report arrived, the time to implement some of the recommendations mentioned had already passed. You didn't make a mistake again?

Mr. CRAWFORD. That was a mistake.

Mr. CUMMINGS. Upon hearing of the actual contamination of vaccine this summer, FDA neither conducted a prompt inspection nor reviewed the company's records. As a result, FDA was caught completely by surprise by the British enforcement action. Was that a mistake?

Mr. CRAWFORD. We did review the company's records.

Mr. CUMMINGS. So no mistake there?

Mr. CRAWFORD. No.

Mr. CUMMINGS. You know, we have a major problem here. We have people in my district who cannot get these flu vaccines that are begging for them; seniors, many of them standing in long lines. But FDA made no mistake. The reason why I asked you these questions is that we cannot deal with a problem unless we accept the fact that we have one, that we made mistakes.

Mr. CRAWFORD. We are working to get more vaccine.

Mr. CUMMINGS. So FDA made no mistakes.

Mr. CRAWFORD. Look——

Mr. CUMMINGS. Yes or no?

Mr. CRAWFORD. The vaccine was contaminated in the final fill. There was no way to know that until October 5, when the final report came through. You can't do that until it gets finished. We didn't make a mistake because we condemned the vaccine; it did not go into U.S. circulation. That was not a mistake. I would do it again.

Mr. CUMMINGS. So you are saying to the people of the United States, as they watch you on C–SPAN, that you all made no mistakes.

Mr. CRAWFORD. As I said, we condemned the vaccine——

Mr. CUMMINGS. Yes or no?

Mr. CRAWFORD [continuing]. And it did not get here. We make mistakes, but we followed the procedures——

Mr. CUMMINGS. No, I am talking about with regard to this.

Mr. CRAWFORD [continuing]. And we took the right action.

Mr. CUMMINGS. No mistakes.

Mr. CRAWFORD. The vaccine didn't get into circulation.

Mr. CUMMINGS. Fine. Apparently, you don't want to answer my question. I asked you a question. I said did you make any mistakes. Did FDA make any mistakes with regard to this?

Mr. CRAWFORD. I already——

Mr. CUMMINGS. Sir, let me tell you something. I have to go back to my district and I have to explain to them why we have a Federal agency that, to me, made some mistakes, but refuses to admit it. At least just say no.

Mr. CRAWFORD. I already told you we made a mistake.

Mr. CUMMINGS. No.

Mr. CRAWFORD. We made a mistake. I can tell you no.

Mr. CUMMINGS. You did? What were the mistakes that you made, so that we can correct them?

Mr. CRAWFORD. We didn't get the report back to them on time in 2003; we were late by a few months, and our procedures call for it to get there in time. We have corrected that procedure, but that was a mistake.

Mr. CUMMINGS. Let me ask you one last question. During the campaign season I noticed one interesting thing that happened. Every time this flu vaccine came up in my district, my opponent jumped up and said that there are not more companies producing it because they are afraid of liability. I heard that over and over again. And then I read in the Washington Post that one of the main reasons why they didn't produce it is because it has a short life span, and they were afraid of spoilage and losing money.

Is that true? Which one is true?

Mr. CRAWFORD. I don't know why they don't enter the U.S. market. I don't know about liability; I think that could be a factor. But they have to remake the vaccine every year, and I am sure that is a factor.

Mr. CUMMINGS. But you are saying you don't know why they don't enter the U.S. market?

Chairman TOM DAVIS. The gentleman's time has expired. Thank you.

Mr. CUMMINGS. He said no. I just want to make sure that is on the record. He doesn't know why they don't enter the U.S. market.

Chairman TOM DAVIS. The gentleman's time has expired. And I don't think it is productive for Members to be screaming at witnesses that are here on their own volition. We all have questions of this.

Mr. CUMMINGS. Mr. Chairman.

Chairman TOM DAVIS. Now I am going to take my 5 minutes.

The FDA basically followed your standard practices in waiting for the failure investigation report, right?

Mr. CRAWFORD. Yes.

Chairman TOM DAVIS. Before proceeding to inspect the Chiron. And Chiron never did produce the report to you until after its license was suspended by the MHRA on October 4th.

Mr. CRAWFORD. That is correct.

Chairman TOM DAVIS. The FDA and MHRA have both told the committee that Chiron had no reason to expect its license would be suspended until it completed its failure investigation report that was provided in draft to MHRA on September 24th.

Mr. CRAWFORD. That is correct.

Chairman TOM DAVIS. Once Chiron's license was suspended, on October 4th, U.S. access to the report and investigation by U.S. authorities was a moot point, although further inspection confirmed the judgment of MHRA, is that correct?

Mr. CRAWFORD. Yes.

Chairman TOM DAVIS. The problems at Chiron are not longstanding ones that FDA should have recognized long ago; Chiron's license was suspended for systematic problems in the facility, such as lack of oversight and execution, but not the specific contamination or other issues addressed in 2003, as you have stated, and as we have gone through and I think the reports are clear, is that correct?

Mr. CRAWFORD. Yes, that is correct.

Chairman TOM DAVIS. The FDA didn't reject the initial recommendation of the team biologics to refer official action on the June 2003 issues?

Mr CRAWFORD. No, we did not.

Chairman TOM DAVIS. And further discussions resulted in full agreement by all of those involved that voluntary action was appropriate, isn't that correct?

Mr. CRAWFORD. That is correct.

Chairman TOM DAVIS. Was there any dissension in that?

Mr. CRAWFORD. No. The team biologics has a very good peer review of the process, and then they reach a consensus.

Chairman TOM DAVIS. And there is no evidence that anyone involved in the process disagreed with the final decision, is there?

Mr. CRAWFORD. No, there is not.

Chairman TOM DAVIS. OK. I appreciate it.

Mr. Mica, did you want to ask.

Mr. MICA. Thank you.

Chairman TOM DAVIS. Well, I am in my 5 minutes. Mr. Shays will get 5 minutes.

Mr. MICA. You know, you have been hammered. You still haven't understood this, because you are the bad guy, and we have to prove you bad.

Mr. CRAWFORD. I am beginning to get the picture, though.

Mr. MICA. OK. But this 2003 mistake that you admitted to, in not responding in time, now the batch of vaccine, when was that produced that proved to be bad, was that in 2003?

Mr. CRAWFORD. That was with reference to the 2003 vaccine, which proved to be good, actually.

Mr. MICA. OK. So the 2003 mistake that you admitted to had nothing to do with the batch in 2004.

Mr. CRAWFORD. Nothing, absolutely nothing.

Mr. MICA. OK. Well, but see, you are bad, and you have to pay, because we don't have the drug companies around; we have less people. Pretty soon you are not going to have anybody to send warnings to. What the hell are you guys going to do over there?

Mr. CRAWFORD. It will be a lonely time for us.

Mr. MICA. But it is kind of sad that it has evolved to this.

I think Mr. Van Hollen had a very good point, though. He is gone now, but we do have lots of seniors that want that. We should be manufacturing this in the United States. And Mr. Waxman is right. Even though he attacked me personally, I have to say he is right. We don't have a liability problem now because we have just about run out of people to sue. So he is right on one account. But you have to adjust liability.

Dr. Gerberding, she went down all of the problems: you have a short shelf life; you don't have a guaranteed market, so people don't produce it; you have regulations that impede the production in the United States; you have a guaranteed purchase program of childhood vaccines that actually pays less than I think the cost, and that has also inhibited the manufacturing in the United States. So it is a host of these issues. And until Congress addresses these issues and changes some of the law regulations that we have in place, in fact, we won't be producing these vaccines in the United States.

Just a quick question, doctor. Wouldn't it be a lot easier for you to keep tabs on these manufacturers if they were in the United States, rather than far-flung around the globe?

Mr. CRAWFORD. It certainly would be easier to get to them. We don't have any overseas locations at FDA, we have to dispatch our teams of inspectors from here.

Mr. MICA. OK.

And guaranteed purchases, Dr. Gerberding, that is also something that needs to be addressed?

Dr. GERBERDING. I don't have the right formula for a solution, but everything is on the table right now, and in order to guarantee a market, that would be one strategy that we could look at to ensure the manufacturers that their vaccine would be purchased.

Mr. MICA. And the government now buys 60 percent of the pediatric vaccines. Is that still the case? That is the information that I have.

Dr. GERBERDING. I believe that is correct, but I can get you the exact percentage.

Mr. MICA. Thank you.

Chairman TOM DAVIS. OK, we are just about up. Thank you.

Let me just add. We had an old saying when I used to practice law, that if you have the facts, you pound the facts; if you have the law, you pound the law; and if you have neither, you pound the table. I think in this it is pretty clear from the record that you have set out earlier today that you followed the appropriate procedures, you followed the appropriate protocols. We may need to tweak those protocols a little bit. I mean, we need to make sure what happened this year should never happen again.

Mr. CRAWFORD. Absolutely.

Chairman TOM DAVIS. And I think we need to have that dialog of how best to prevent it. It seems to me that the most basic thing we can do is make sure there are more suppliers. As Mr. Sanders and others have pointed out, there are foreign suppliers who haven't asked for U.S. recognition, but we need to get them into our markets and have you out there inspecting them. And if we do

that, at least we have some guarantee of alternate sources of supply. There are other issues we need to look at, but we will talk about that.

Mr. Shays has 5 minutes a little later, and we will talk about that.

Ms. Watson has not had her 5 minutes yet. Diane has been patiently waiting over there.

Ms. Watson, you are recognized for 5 minutes.

Ms. WATSON. Thank you, Mr. Chairman, very much.

And thank you, doctor, for being willing to sit on the hot seat. We are not going to talk about that or good guys. I just would hope that you would clarify some things for us. So I am going to raise two issues, and then you can just address them together.

The first thing, I understand that Chiron is based in my own State of California, yet we manufacture in the United Kingdom for the U.S. market, and I am wondering why we could not start building a plant in California, why Chiron could not. That ought to be something that we ought to be talking to them about. And Aventis, I understand, is a French firm, but they manufacture in Pennsylvania.

So is it possible to produce the supplies that we are going to need? And I will imagine our need will be greater in 2005 in California and Pennsylvania. You can answer that after I finish with my next comment.

The next comment is that I understand in June 2003, after the inspection, the company asked to meet with the FDA. Is it true or not that the FDA refused to meet with Chiron to discuss its problems? So can you clarify what is going on? It is essential, if they are one of two producers for the U.S. market, that we be communicating with each other.

So can you clarify those issues for me, please?

Mr. CRAWFORD. Yes. We did meet with them. I have actually met with them myself, so that is not correct.

Ms. WATSON. Can you give me a time?

Mr. CRAWFORD. We can supply that for the record, yes.

Ms. WATSON. Has it been after 2003?

Mr. CRAWFORD. Yes. And with respect to the fact that there are no vaccine production facilities owned by American firms in the United States, I believe Chiron is going to testify on the next panel, and you may wish to ask them. I think what guides them to seek facilities elsewhere is because the facility is available. In other words, I believe in mid-2003 Chiron actually acquired this plant from another company, and they didn't even own it until that point. The facility that is in Pennsylvania I also believe was previously owned by another corporation. So I think even though a French company manufactures there is because the plant was present.

Now, what do we do about getting plants built in the United States? That is beyond my authority or expertise, but I would think what we are doing will help some, and that is we are engaging the CEOs of all the companies in the world that produce flu vaccine, and we are telling them that FDA has a commitment to help them get up-line and get moving to either enter the U.S. market or to build a facility in the United States. We will help them with what-

ever we can do. We can't force them to do that, though, and that is why I responded as I did to the last questioner.

Ms. WATSON. I think that as the Federal Drug Administration, and with the threat of maybe a biological war, a threat of biological vaccines coming in that are very toxic, I would think that the FDA would want to suggest that we have legislation requiring that we develop our own plants under the regulations that you already have. I see the need as being tremendous, with the threat that is facing the United States and the rest of the world from the terrorists. We need to be ready. I would think that would be a readiness plan that would be recommended from the FDA. We should never find ourselves in this position again.

And as Elijah Cummings said, people are coming into my office in the center of Los Angeles in tears, and they are rushing around to see if they can find a place to get their flu shots. And I am telling them don't get one, it probably will give you the flu, because they do inject some of the, as I understand, the microbes.

But please, please, as FDA, don't wait for us as the legislators to do it; you need to come with a strong recommendation and we need to get the building of the plants and the distribution of these needed vaccines right here in the United States.

Thank you, Dr. Crawford.

Mr. CRAWFORD. Thank you.

Dr. GERBERDING. Mr. Chairman, may I just say one thing?

Chairman TOM DAVIS. Yes, Dr. Gerberding. Sure.

Dr. GERBERDING. I would just like to emphasize that the injectable flu vaccine does not contain live virus that causes the flu; there is no risk of getting the flu from the vaccine. The nasal vaccine does contain a weak flu virus, so there is a theoretical risk of getting flu from that product, but not the injectable vaccine.

Ms. WATSON. Let me just respond by saying regardless, I think they ought to be manufactured here, the nasal or the injectable. We ought not to depend on other nations for our tremendous need.

Dr. GERBERDING. I absolutely agree with you on that. Thank you.

Ms. WATSON. Thank you.

Chairman TOM DAVIS. Mr. Shays, you are recognized for 5 minutes.

Mr. SHAYS. I thank the gentleman.

It is a wild circumstance. We have an American company whose product made in England and we have a French company whose product is made in Pennsylvania. And what I am interested to know, Dr. Crawford, is if you had realized even 5 months earlier that we had a problem, there would have been no solution, or would we have been able to go out and request vaccines from other places and been able to deal with this problem?

Mr. CRAWFORD. The eggs, which are chicken eggs, are actually——

Mr. SHAYS. I need a short answer.

Mr. CRAWFORD. It started too early, so we couldn't have done anything about it.

Mr. SHAYS. So it speaks to a much bigger issue.

Mr. CRAWFORD. Absolutely.

Mr. SHAYS. I just want to align myself with Mr. Davis and also Mr. Mica. This is a huge problem, but the fault does not rest at

your doorstep; it rests right here in Congress, working with the three of you.

I would like to ask Dr. Gerberding, on October 25, 2004, the CDC introduced a secure electronic system to display influenza vaccine dosage distribution information called the Flu Vaccine Finder. This dataset is only available to State health officials. Has the Flu Vaccine Finder proven to be an effective tool for States to identify and reallocate available vaccines?

Dr. GERBERDING. The Flu Vaccine Finder is an unprecedented way for States to see the proprietary information about vaccine delivery in their jurisdiction. I believe they are finding it to be extremely helpful. The feedback we have received so far has been enthusiastic and with great relief. They can finally get their hands on the information about distribution planning that they need. We are working to make that same kind of information available to people at the local health department level as well; that just takes longer because there are several thousand of them.

Mr. SHAYS. Before I ask you the next question, I want to say that the imminent biological threat facing the United States I think is pandemic influenza, as a mutated viral form has caught the world unaware in the past, and it will do so in the future. SARs was a huge opportunity for us to see how we would deal with this issue. It was involuntary and it was life-threatening, and it was extraordinarily serious. I think it points out persistent weaknesses in public health surveillance and vaccine production surge capacity to meet emerging threats, and I would like to know if you agree.

Dr. GERBERDING. I agree. But I also think that the investments we have made and the lessons we learned from SARs have been very helpful to us in dealing with this current flu season situation, and we are learning lessons from this situation that will help us be even more prepared for a pandemic flu. In fact, that is part of our mission right now, is to look at the distribution process, to look at our detection capabilities, look at our surge and make sure that we are learning from that so that if we see pandemic flu emerge, we can be better prepared.

Mr. SHAYS. So what I want to ask the three of you is I am asking do we need a new mechanism, new incentives to guarantee to that adequate numbers of safe and effective flu vaccines are produced and delivered annually? Just in this more particular case I guess the answer is yes. And then with the very short period of time remaining, tell me what that is.

Dr. FAUCI. One of the things from a research standpoint, very briefly, is to provide the advanced technologies to allow the companies to be able to get a head start, since we obviously have to partner with them to get the vaccine developed and out in an emergency situation. I mentioned a couple of them in my presentation. And that is one of the ways we can do it, by providing the technology through the science. That is one of several ways.

Mr. SHAYS. And provide economic incentives that they are willing to do that.

Dr. FAUCI. Oh, absolutely. And that gets to the point that you were making There are four or five issues that we need to do. It is a risky business; it is not a high profit business. We have to not only provide the technologies that I mentioned, but some of the

things that Dr. Gerberding early on mentioned and Mr. Mica questioned, something like guaranteed purchases, cutting down some of the red tape which we call regulatory relief. And liability fits in there. It may not be the biggest one, but it is one of several things we can do.

Mr. SHAYS. I agree.

Chairman TOM DAVIS. Thank you very much.

Well, let me say to this panel thank you. Dr. Crawford, that is it. We don't have any more questions. I know you are sorry to hear that. You have accorded yourself well. All of you have. And we appreciate very much your time and your expertise on this. You are no strangers to this committee. We look forward to working with you in the future as we consider these issues. Thank you very much.

The committee will take about a 3-minute recess as we get ready for our next panel.

[Recess.]

Chairman TOM DAVIS. Thank you. We are moving to our next panel.

I want to thank our witnesses for appearing. Invited to join us on our second panel are two vaccine manufacturers to discuss vaccine production capacities to respond to the shortage crisis in ways to ensure a stable annual flu vaccine supply. Dr. Howard Pien, who is the president and chief executive officer and chairman of the board of Chiron, will be providing testimony. We also have Kathleen Coelingh of MedImmune, which manufacturers the nasal spray vaccine, FluMist, which was referred to earlier. And Dr. Robert Stroube, who is the Virginia State health commissioner, also joins us. He is here on behalf of the Association for State and Territorial Health Officials to provide an assessment of State and local public health departments' ability to respond adequately to the vaccine shortage. And last but not least, Dr. Jerome Klein is here from the Boston University School of Medicine. He will be providing a more academic perspective into issues surrounding the annual influenza vaccine.

It is our policy that we swear everybody in before you testify, so if you would rise with me and raise your right hands.

[Witnesses sworn.]

Chairman TOM DAVIS. Thank you.

Let the record show everybody is here on their own volition. We appreciate very much your being with us today. I think you know the rules; your entire testimony is in the record. You have 5 minutes to say whatever you want. I think you know when the lights come up.

Dr. Pien, we will start with you. And I know this has been an interesting 6 months or so for you, but we appreciate your working with us, working with our committee staff here and in London, and we are pleased to have you here. Thank you.

STATEMENTS OF HOWARD PIEN, PRESIDENT, CHIEF EXECUTIVE OFFICER, AND CHAIRMAN OF THE BOARD, CHIRON CORP.; KATHLEEN COELINGH, SENIOR DIRECTOR, REGULATORY AND SCIENTIFIC AFFAIRS, MEDIMMUNE, INC.; DR. ROBERT STROUBE, VIRGINIA STATE HEALTH COMMISSIONER, ASSOCIATION OF STATE AND TERRITORIAL HEALTH OFFICIALS; AND DR. JEROME KLEIN, PROFESSOR OF PEDIATRICS, BOSTON UNIVERSITY SCHOOL OF MEDICINE

Mr. PIEN. Thank you, Chairman Davis and members of this committee. I welcome the opportunity to appear at this hearing.

In light of Chiron's strong tradition of commitment to global public health, our vaccine division's inability to provide influenza vaccine to the United States for this season has been a painful experience from which we are all learning a great deal. As we have said on numerous occasions in the past, we profoundly regret that we have been unable to supply influenza vaccine for this season. And we appreciate the opportunity to engage in these very important discussions.

I respectfully suggest that the lessons learned from this year's experience provide an excellent opportunity to reflect on the critically important policy initiatives that the 109th Congress should consider to ensure a reliable and stable influenza vaccine supply for the United States in the future.

I will focus my remarks on three key messages: what we are doing, what is our prospect, and what are the policy considerations that have emerged from this experience.

First, Chiron Vaccines is proceeding expeditiously in implementing internal changes and devoting resources to enable it to regain its U.K. vaccines manufacturing license and to address the concerns raised by the FDA. In the past several weeks, Chiron Vaccines has developed a plan to implement a series of fundamental personnel changes that will restructure the management of our Liverpool operations. These personnel changes will leverage the strength of Chiron's existing global management team and will be supplemented by new management to help take us forward in managing the Liverpool facility. These changes will maximize our ability to enhance our prospect to meet the challenge of returning to influenza vaccine manufacturing for the 2005–2006 season.

We have assembled a world-class international team of 70 internal and external individuals with expertise in quality control, quality assurance, manufacturing, and regulatory standards to conceptualize and implement a remediation plan. We have retained external consultants who have substantial experience with the United States and the U.K. regulatory standards. Most importantly, upon the approval of the implementation plan by our board of directors, this team will be empowered to make changes that will restore the confidence of our regulators, both here and in the United Kingdom.

Also, effective November 3rd, I reorganized Chiron's senior management team to allow me to focus more attention on overseeing the Vaccines Division's remediation activities at Liverpool. To that end, I have appointed an interim chief operating officer of Chiron in Jack Goldstein, previously our president of the Blood Testing Di-

vision. Starting November 4th, Jack began overseeing our operations other than those related to Fluvirin remediation.

To my second point. By devoting these resources to the remediation of our Liverpool facility, we expect to meet and exceed the required responses to the MHRA and the FDA observations raised in their respective inspections.

Chiron Vaccines acquired the Liverpool facility in July 2003. Although both the regulatory community and ourselves recognized it was a somewhat older facility, we promptly committed to replacing the influenza vaccine production plant with a state-of-the-art adjacent facility estimated to cost $100 million, which is under construction. We also proceeded to address a number of the concerns identified by the FDA in its June 2003 inspection conducted when Liverpool was under previous ownership. At present, in coordination with both the MHRA and the FDA, we are close to finalizing a detailed remediation plan for our Liverpool facility. The plan covers a range of enhancements to our manufacturing processes, quality systems, and structure for management oversight. Subject to the concurrence of both regulatory authorities and approval by our board of directors, we will implement this plan expeditiously, with the hope and the aim of supplying influenza vaccine next season.

Our ability to regain our U.K. influenza vaccine manufacturing license in time to participate in vaccine production next year is mission-critical for Chiron Vaccines. This plan addresses quality systems in a holistic manner and is proposed with the aim of exceeding the specific regulatory observations made last month by the MHRA and the FDA. The plan covers personnel, processes, equipment, systems, and infrastructure. The organizational changes will enable us to entrench a culture of quality where employee performance is correlated clear and quantitated performance metrics.

To successfully achieve its remediation objectives and to be able to provide influenza vaccine next year, extraordinarily close coordination between the MHRA and the FDA will be needed. In the meetings that we have held with these regulatory authorities since October 5th, we are heartened by the encouragement we have received. Having said that, it is important to add two cautionary notes. In light of the broad and ambitious scope of our remediation plan, there can be no conclusive assurance that we will be able to meet expectations of the MHRA and the FDA by March 2005, which will be the start of full-scale manufacturing season. Moreover, because the regulators' GNP standards are ever-rising, we cannot say definitively whether we will be able to meet them in future years.

To my third and final point. This year's experience provided lessons that can enable us to strengthen our national public policies with regard to interpandemic and pandemic influenza. We know we must address short-term and long-term policy objectives that assure a stable supply of influenza vaccine that drive uptake for vaccine and that establish manufacturing capacity within the United States. In the so-called normal influenza season, a stable vaccine supply for the U.S. market is dependent on diversifying the manufacturing base, which is in turn driven by an environment conducive to multiple manufacturers. This environment should have the

following characteristics: (1) sufficient demand to enhance production capacity; (2) pricing and reimbursement that justify investments in maintaining and expanding existing production capacity; (3) a regulatory pathway that fosters innovation in new technologies; and (4) mechanisms to reasonably protect vaccine manufacturers from liability claims.

Marketing of influenza vaccine is dependent upon an effective public and private partnership that improves vaccination rates by raising awareness, dispelling myth, and extending the immunization season. In the long-term in order to effectively address our public health needs in the event of a global influenza pandemic, a strong public-private partnership is paramount, particularly to prioritize and allocate influenza vaccine in the event of a supply challenge. The essential ingredients for meeting this challenge are evident: information-sharing, partnership, frequent communication, and hard work. The public health system is coping with the challenges, and I believe will emerge stronger from this experience, with a clearer focus on strengthening our influenza immunization infrastructure and creating a sustainable influenza market. The men and women of the public health service have demonstrated incredible leadership in addressing public distress and in getting vaccine to those who need it most in the current supply shortage.

With that as a backdrop, to increase manufacturing capacity in the United States, the government should begin now to invite additional manufacturers into the U.S. market and to provide appropriate financial incentives and clear regulatory guidance. Experience teaches us, as you said, Mr. Chairman, that establishing this capacity likely will take several years. However, events occurring with regard to the avian flu in the pacific realm indicate that the pandemic clock is already ticking; thus, we cannot afford any delay.

I ask, respectfully, that my written testimony be also included as part of the record, and I am prepared to answer any questions.

Chairman TOM DAVIS. Without objection, the entire testimony of all of you will be a part of the record.

[The prepared statement of Mr. Pien follows:]

CHIRON

Statement Presented To

Committee on Government Reform

United States House of Representatives

By Howard Pien

President and CEO

Chiron Corporation

November 17th, 2004

Introduction

Mr. Chairman, Members of the Committee: Thank you for the opportunity to provide a statement to the Committee on Government Reform at today's hearing. I am Howard Pien, president and CEO of Chiron Corporation, a global biotechnology company headquartered in Emeryville, California with 2003 revenues of $1.75 billion. Founded in California in 1981, Chiron is composed of three business units: BioPharmaceuticals, Blood Testing and Vaccines. Chiron is dedicated to research and innovation addressing global public health challenges. Through Chiron's breakthrough research discoveries in the fields of hepatitis B virus, human immunodeficiency virus and hepatitis C virus, millions of potentially fatal infections have been prevented.

Overview of Chiron Vaccines

Chiron is the fifth-largest vaccines producer in the world, with sales of $678 million in 2003. Chiron Vaccines produces pediatric and adult vaccines to prevent life-threatening illnesses. These vaccines have protected millions of people globally from *N. Meningitidis* Group C, polio, measles and other potentially fatal diseases. Chiron is a leading supplier of oral polio vaccine, producing more than 800 million doses annually to support global polio eradication efforts. Our rich heritage in vaccines is traced to the three European manufacturers Chiron has acquired over the past two decades, all of which were founded 100 or more years ago. The company has production facilities in Liverpool, United Kingdom; Siena, Italy; Marburg, Germany; and Ankleshwar, India; and it carries out research in Siena, Marburg and Emeryville. Chiron has a successful record of product development, including the launch of the first recombinant vaccine against pertussis, the first adjuvanted influenza vaccine and a conjugate vaccine against *N. Meningitidis* Group C.

Chiron currently has two vaccines licensed in the United States: Fluvirin® influenza vaccine, one of only two injectable influenza vaccines approved by the U.S. Food and Drug Administration (FDA), and RabAvert® rabies vaccine. Fluvirin is indicated for immunization against the influenza vaccine strains contained in the vaccine for persons of four years of age and older. Chiron also supplies diphtheria and tetanus (DT) concentrate to GlaxoSmithKline for use in its DT-containing vaccines licensed by the FDA.[1]

Influenza Immunization

Vaccination of persons at risk from the complications of influenza is a key public health strategy in preventing morbidity and mortality due to the disease. Based on data from the 1990s, the U.S. Centers for Disease Control and Prevention (CDC) have estimated that influenza causes an average of approximately 36,000 deaths and 200,000 hospitalizations per year in the United States, with 90 percent of the mortality occurring in adults of ages 65 years and older.[2,3]. In order to minimize the burden of disease caused by the annual influenza epidemic, the following requirements, best achieved through public-private partnerships, must be met:

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[1] Infanrix (DtaP) & Pediarix (DtaP-HepB-IPV)
[2] Source: Morbidity and Mortality Weekly Report 2003, Vol. 52 RR8
[3] Source: *JAMA*. 2004;292:1333-1340

- An adequate, uninterrupted and sustainable supply of influenza vaccine to protect the population.
- Appropriate mechanisms to ensure delivery of the vaccine to the target populations.
- High public awareness on the need for immunization to ensure uptake of the vaccine by the target population.

Chiron Support for Handling the Challenges of this Season

Prior to October 5th, advance planning of activities for the 2004-2005 influenza season by the public and private sectors was based on the anticipation of a record supply of influenza vaccine, along with aggressive vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP) and increased public interest in influenza immunization following heightened awareness during the 2003-2004 season. The challenges the public sector expected for the upcoming influenza season involved fulfilling the new Vaccines for Children (VFC) entitlement for children ages 6-23 months old and people under 18 years of age who are close contacts of infants ages 0-23 months, as well as reducing ethnic and geographic disparities in coverage rates.

Over the past four weeks the public and private sectors under the leadership of the CDC have worked diligently to develop and implement a plan to meet the unanticipated supply shortage. One of the key issues that needed to be addressed was allocation of the remaining doses of influenza vaccine; accordingly, a plan was developed to distribute scarce influenza vaccine to providers most likely to be able to reach high-risk patients. Clearly, a key piece of information in developing the plan was learning the destinations and volumes that had been projected for Fluvirin. While Chiron was not able to provide information down to the level of end-user as it does not supply vaccine directly to physicians and clinics, it was able to assist the CDC by facilitating contact with the seven distributors who handle Fluvirin, as well as providing additional information requested by the CDC. Chiron has chosen a distributor based model as this ensures that its influenza vaccine can be rapidly and efficiently distributed to thousands of sites all across the country.

The primary focus of Chiron's activities over the past few weeks has been to work closely with the regulatory authorities to develop a remediation plan to address the issues the two regulatory agencies have raised about its Liverpool facility. Chiron's primary concern at this time is to be in a position to supply influenza vaccine to the United States for the 2005 - 2006 influenza season in order to ensure that there is an adequate supply of vaccine available.

Chiron Remediation Activities

Chiron is developing a robust remediation plan that, pending approval by the Chiron Board of Directors, will set Chiron on the path towards achieving our goals in the right time frame. We have discussed our with both the FDA and the UK Medicines Healthcare

products Regulatory Agency (MHRA), and Chiron plans to continue working with both agencies to achieve our common goal of ensuring the Liverpool facility is in a position to supply influenza vaccine next season.

The comprehensive remediation plan developed addresses quality systems in a holistic manner, going beyond merely responding to specific regulatory observations. Our remediation activities are concentrated in three primary areas:

- Manufacturing: Manufacturing processes, practices and techniques.
- Quality systems: The quality systems used in the manufacturing, testing, and lot evaluation process.
- Governance: Management of people and handling of issues.

Within each manufacturing area Chiron intends to address issues surrounding: what it does, how it does it, who does it and why, what resources are needed, and how the quality of the output is checked.

Leadership is a critical success factor in executing a task as complex as the remediation plan in the short time frame required. Effective November 3, I reorganized Chiron's senior management team to allow me to focus more attention on overseeing the remediation activities and quality improvement. We have created the position of Chief Operating Officer on an interim basis, and Chiron's COO will oversee other parts of our diverse organization to ensure that Liverpool remediation is my top corporate priority for Vaccines.

Our internal experts, transferred from Chiron Corporation business units across the globe, and external consultants will focus on addressing the underlying, fundamental issues that have been uncovered and on developing a robust quality system at our Liverpool facility. Chiron understands the urgency of the situation and is acting with expediency and diligence to redress our Good Manufacturing Practices (GMP) deviations and to execute effectively a robust remediation plan.

Influenza Vaccine Supply Overview

Ensuring an adequate supply of influenza vaccine for the United States is a key component of any strategy for reducing the burden of influenza disease. A critical success factor for securing an uninterrupted influenza vaccine supply over the long term is the creation of a sustainable market for influenza vaccine: one where favorable conditions exist to enable manufacturers to invest and expand. The market conditions required to create a positive environment include but are not limited to:

- Sufficient demand for the vaccine to ensure that production capacity for the vaccine is utilized.
- Levels of pricing for the vaccine that justify investments by producers in maintaining existing production capacity and, if required, encourage investment in additional capacity.

- A regulatory regime that fosters innovation in the enhancement of existing technologies and development of new technologies while ensuring the safety of available vaccines.
- A mechanism for protecting influenza vaccine producers from liability issues.

In the 1990s, the environment was not conducive to encouraging investment in influenza vaccine manufacturing capacity due to a combination of factors, primarily low pricing and stagnant demand. This environment was an important contribution to the exit of several manufacturers of influenza vaccine resulting in supply constraints on the US market. Over the last few years, however, the trend has been reversing. The market has expanded due to broadened recommendations on influenza immunization by the ACIP to include individuals between 50 and 64 years of age, healthy children between 6 and 23 months of age, and close contacts of children aged up to 23 months of age[4]. Pricing of influenza vaccines has reached a level that allows manufacturers to invest in maintaining facilities to meet rising FDA standards and in expanding manufacturing capacity in order to meet the increased demand. Finally, reimbursement rates for providing influenza vaccine injections have increased to levels at which physicians are encouraged to actively immunize patients, raising coverage rates.

The changes in the business environment, especially the price increases that have occurred over the past three years, have reversed the trend of decreasing manufacturing capacity. Producers are investing in capacity increases, upgrading facilities and licensing cutting-edge technologies for the United States. However, given the nature of biologics manufacturing, there is inevitably a lag between the decision to invest and improved capacity as a result of that investment. The United States is only now beginning to see the impact of the positive changes in market dynamics that occurred a few years ago. For example, Chiron has committed $100 million dollars to replace its existing influenza bulk manufacturing facility with a new "state of the art" facility[5] to complement the secondary manufacturing facility opened in 1998. This commitment is being made to support Chiron's ability to supply Fluvirin to the United States and to add incremental capacity, if required, until new technologies such as cell-culture production are sufficient to meet the needs of the United States.

Diversification of Influenza Vaccine Supply

The supply shortage that the United States currently faces this season has served to highlight an additional dimension required for this country to achieve ***"influenza vaccine security,"*** diversification of sources of supply. ***"Influenza vaccine security"*** is defined as access to an uninterrupted and sustainable supply of safe and effective influenza vaccine to satisfy annual demand under routine epidemic circumstances.

Prior to this season, the focus of public health had been on volume of production: ensuring that production capacity was at a level sufficient to make certain that an adequate supply of influenza vaccine was available to meet demand in inter-pandemic

[4] Source: Morbidity and Mortality Weekly Report 2004 Vol 54: RR6.
[5] A new fill/finish facility was completed a few years ago.

years. Arguably, the influenza vaccine supply situation was much less fragile than for many other commonly used vaccines in the United States. The Institute of Medicine Report "Financing of Vaccines in the 21st Century; Assuring Access and Availability"[6] highlighted the fact that for six of the recommended vaccines[7] in the United States, there is a single source of supply. Should a manufacturer of one of these vaccines experience production problems or other disruptions, there is no backup capacity available. This situation creates significant potential for supply interruptions, and, indeed, these have occurred over the past few years. In 2001 and 2002, eight of the 11 recommended childhood vaccines were in short supply.[8] These shortages had an impact on immunization policy in the United States, forcing the ACIP to temporarily revise its recommendations on pneumococcal conjugate vaccine and diphtheria, tetanus and pertussis (DtaP) and to recommend that varicella (chicken pox) immunization be pushed back to 18-24 months from 12-18 months. In contrast, there are three sources of supply for influenza vaccine, making a complete disruption of supply an unlikely event. Regrettably, the events of this season have highlighted a flaw in this argument, related to the nature of influenza vaccine production and use.

This season's experience has shown the risk of dependence on two production facilities to supply the majority of influenza vaccine for the United States. A significant problem at either of the two facilities could reduce supply by as much as 50 percent, creating significant challenges for the public health infrastructure. Essentially, while a complete disruption of supply is unlikely, the potential for a major shortfall exists if only two facilities provide approximately 95 percent of the vaccine used in the United States.

Due to the seasonal nature of influenza immunization, the inability to stockpile vaccine and the cycle-times for influenza vaccine production, the public health system has little time to react to such a shortfall. It is not possible to secure alternative sources of supply of influenza vaccine in the volumes that would be required, as little excess capacity is available on the global market. Therefore, based on the lessons learned from this season, diversification of influenza supply, reducing the dependence of the United States on the two production facilities that currently supply 95 percent of demand, is an important component if the United States is to achieve influenza vaccine security.

Accomplishing the diversification of the manufacturing base of influenza vaccine supply is not a simple task and poses significant short and long-term challenges. In the short-term, this requires identification of existing suppliers who not only have spare capacity but also are capable of meeting FDA standards in terms of clinical data and compliance with U.S. standards of GMP. Once such suppliers are identified they must go through a review of their data by the FDA. Expediting this process while ensuring that vaccines meet U.S. regulatory standards represents a significant challenge. Simply building a new

[6] Institute of Medicine, August 2003
[7] Tetanus-diphtheria, measles-mumps-rubella, varicella (chicken pox), pneumococcal conjugate, meningococcal polysaccharide, pneumococcal polysaccharide
[8] USA Today, February 18, 2002

production facility for the United States is not a short-term option, as it would take five or more years to develop and license a new influenza vaccine production facility[9].

In the long term, the challenge for diversification of the manufacturing base is even more complex, as any solution must be sustainable if it is to ensure an uninterrupted supply of influenza vaccine. Attracting new entrants into the influenza market is only the first step to reducing the chances of disruption. Conditions must be created such that both the new entrants and the existing suppliers remain in the market over the long haul. The challenge therefore goes beyond finding new entrants; the challenge is to create a market environment that is conducive to supporting multiple manufacturers of influenza vaccine. Recent experience serves to illustrate the inherent difficulty of accomplishing this objective. In the late 1990s the United States had four licensed suppliers of influenza vaccine, three of which were located in the United States. Due to market conditions two of the four ceased production. Similar lessons can be gleaned from the experience with another vaccine, tetanus-diphtheria (Td) where prices in the range of $1.00 per dose led to the exit of several manufacturers leaving a single source of supply[10]. Many of the lessons learned from these experiences are applicable to the future of influenza vaccines. It is essential that vaccine prices are at a level sufficient for producers to invest in maintaining and upgrading manufacturing facilities, and that sufficient demand for influenza vaccine is created to ensure utilization of existing production capacity and development of additional capacity. If these conditions are not met over the long-term history will repeat itself, and the number of manufacturers of influenza vaccine will inevitably shrink as the market will not be attractive enough to justify continued investment.

In the last few years, the United States has come a long way towards creating incentives that encourage manufacturers to invest in capacity and physicians to acquire and administer the influenza vaccine. Appropriate reimbursement rates for influenza vaccine purchase and administration are important, particularly through Medicare as the vaccine is universally recommended for those sixty-five years of age and older. Therefore, the decision by the United States Congress to continue reimbursing the vaccine at 95 percent of the Average Wholesale Price (AWP) and to continue the current practice of updating this reimbursement rate on a quarterly basis as established in the Medicare Modernization Act was extremely important in creating a positive environment. The price that the Federal Government has negotiated for purchase of the vaccine through its Vaccines for Children program, which will be expanding its purchase of influenza vaccine due to the new recommendations, also sends a strong signal to manufacturers that there is recognition that pricing of influenza vaccine must be at a level that permits continued investment by producers.

Administration fees are an important mechanism for encouraging demand for influenza vaccine, as they can create an incentive for physicians to actively immunize their patients. The trends in this area over the last few years, such as the increased focus that

[9] Source: Chiron internal estimate.

[10] Sanofi-Aventis is the sole source of supply although small quantities of tetanus vaccine are available from the Massachusetts Public Health Biologic Lab.

Centers for Medicare and Medicaid Services (CMS) has placed on prevention and preventive health services, are extremely encouraging. In 2003, CMS increased administration rates by roughly 90 percent to between $6.00 and $8.00 from less than $4.00, motivating physicians to actively immunize their patients. On November 3, CMS announced that in 2005 it will further increase payment rates to physicians for administration to $18.00[11]. In addition, physicians will now be paid for performing the injections even when they are performed as part of other Medicare-covered services, which was not permitted previously.

Demand for Influenza Vaccine

Recommendations, *"who should get the vaccine"*, and coverage rates, *"who actually gets the vaccine"*, are two significant factors that generate demand for influenza vaccine. Therefore, having the right recommendations in place and making the programs, infrastructure and incentives available to achieve high coverage rates are crucial factors in creating an attractive environment for manufacturers of influenza vaccine. These factors are key to driving demand and demand will drive supply.

Currently, United States recommendations are fairly broad compared to most countries[12]. At present roughly 60 percent of the U.S. population is covered by the recommendations, and it is estimated that 185 million individuals fall into the recommended categories. Over the last few years, the ACIP recommendations on influenza vaccine have been expanded with the addition of additional cohorts. In 2000, the ACIP recommended immunization for individuals between 50 and 64 years of age because of the prevalence of high-risk conditions in this group. Influenza vaccine was recommended for this entire age group to increase the low vaccination rates among persons in this age group with high-risk conditions[13]. In 2004, influenza immunization was recommended for infants between 6 and 23 months of age, primarily due to the increased risk of morbidity and mortality in this age group, and close contacts of infants up to 23 months of age. In the future, the recommendations may be broadened even further. The ACIP has added language to its Recommendations on Prevention & Control of Influenza stating "*ACIP plans to review new vaccination strategies for improving prevention and control of influenza including the possibility of expanding recommendations for use of influenza vaccines*"[14].

Recommendations represent the first step in creating demand. Achieving high coverage rates is the critical second step to generating demand for influenza vaccine and, while progress has been made, the United States still has a long way to go in implementing its recommendations. As mentioned in the previous paragraph, 185 million Americans are

[11] Source: CMS Office of External Affairs Press Release November 3, 2004

[12] Most major European countries, for example, recommend vaccination in individuals 65 and older and high risk groups only.

[13] Age-based strategies are more successful in increasing vaccine coverage than patient-selection strategies based on medical conditions. In addition, individuals aged between 50 and 64 years without high-risk conditions also receive benefit from vaccination in the form of decreased rates of influenza illness, decreased work absenteeism, and reduced need for medical visits and medication.

[14] Source: Morbidity and Mortality Weekly Report Volume 53

covered by the recommendations, yet in 2003-2004 only 83 million Americans were vaccinated, which represented the highest immunization rate ever for influenza immunization[15]. Progress has been made in raising immunization coverage rates, particularly in individuals aged 65 and older. However, significant improvements are needed, particularly for individuals between 50 and 64 years of age, infants aged 6-23 months, and children and healthy adults in close contact with people at high risk.

Over the last decade, the United States has had success in raising immunization coverage rates for individuals above 65 years of age. Data analyzed from the Behavioral Risk Factor Surveillance System (BRFSS) in 1993 indicated that 50 percent of respondents reported having received influenza vaccine compared to 66 percent in 2002[16]. This represents significant progress but is still below the 90 percent goal set for non-institutionalized adults in the Healthy People 2010 Objectives[17] and has remained level since 1997.[18] Continued investment in patient education and ensuring access to vaccine will be required if coverage rates are to continue to increase for individuals 65 years of age and older. Achieving higher coverage rates will increase in importance over the next few years as influenza is expected to have an increasingly serious impact in the United States due to the aging population. Therefore, having effective strategies in place to prevent the disease through immunization will become increasingly important if the burden of disease is not to increase.

Individuals between 50-64 years of age are another population that benefit significantly from influenza immunization as this population has an increased prevalence of high-risk conditions.[19] Despite the universal recommendation being in place for several seasons only 36 percent of respondents between 50 and 64 years of age in the 2002 BRFSS reported having received influenza vaccine during the previous 12 months, well below the level of respondents above 65 years of age. Significant efforts need to be invested in reaching this age group for the following reasons. First, roughly one third of the individuals in this age group are estimated to suffer from conditions such as chronic disorders of the pulmonary or cardiovascular systems, including asthma and metabolic diseases such as diabetes that put them at higher risk of complications due to influenza. Second, in the longer term, achieving high influenza coverage rates in this age group will translate to future higher coverage rates in the 65 and older population. It is likely that an individual who is in the habit of getting an annual influenza vaccine is likely to continue to do so as he or she ages.

As mentioned previously the ACIP included influenza immunization in the routine pediatric immunization calendar for the first time this season. Therefore, it is too soon to assess coverage rates in this cohort. However, a baseline is provided by data collected by the CDC in the 2002 and 2003, when the recommendations encouraged that, when

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[15] Source: CDC

[16] Source: Morbidity and Mortality Weekly Report 1996, Vol 45 No 40; Morbidity and Mortality Report 2003, Vol 52 No 41

[17] Objective no 14.29 at www.health.gov/healthypeople/

[18] Source: Morbidity and Mortality Weekly Report 2003, Vol 52 No 41

[19] Approximately 30 percent of the 42 million persons in the United States between 50 and 64 years of age have one or more high-risk medical conditions.

feasible, children 6 to 23 months of age receive influenza vaccine each season.[20] Roughly four percent of children received two doses of influenza vaccine while approximately seven percent received at least a single dose. This suggests that significant efforts will be required to raise coverage rates in the pediatric population to levels that are similar for other routinely recommended pediatric vaccines which, in 2003, ranged from approximately 70-90 percent[21]. However, given the successes that the United States has had in adding new antigens to the pediatric immunization schedule over the last few years, it seems safe to assume that this goal will eventually be reached, reducing the burden of influenza disease in children.

Immunization of contacts of high-risk individuals represents an important strategy for protection of persons at high-risk for complications from influenza. Persons who are clinically or sub-clinically infected can transmit influenza virus to persons at high risk for complications from influenza. Decreasing transmission of influenza from caregivers and household contacts to persons at high risk might therefore cause a reduction in influenza-related deaths and hospitalization among high-risk populations. Health-care workers (HCWs), due to the nature of their occupation, are often in contact with high-risk individuals and therefore the ACIP and other major medical groups and nursing organizations have recommended that HCWs should be vaccinated against influenza. Despite the recommendations, coverage rates among HCWs are less than 40 percent.[22] Chiron believes that significant efforts need to be devoted to increasing immunization coverage rates in this group. First, improving coverage rates will protect health-care workers, their patients and communities. This will improve prevention, patient safety and reduce the disease burden. Second, health care workers are an important source of information on immunization to the general population and must lead by example. An unvaccinated healthcare worker is not a credible advocate for immunization. Therefore, a first step to convincing the general public to get immunized against influenza is ensuring that health care workers are vaccinated.

In order to raise coverage rates among health care workers Chiron believes the following is needed:

- HCWs should be provided with easy access to influenza vaccine.
- Resources should be committed to institutionalizing immunization of HCWs in their workplace.
- Professional health care organizations should develop policies to support immunization of HCWs and encourage constituents to educate HCWs about the benefits of immunization.
- HCWs influenza immunization rates should be regularly measured and reported.

In this context, Chiron supports the recommendations made by the National Foundation of Infectious Disease in its call to action, *Influenza Immunization Among*

[20] Source: Morbidity and Mortality Weekly Report 2004, Vol 53 No 37
[21] Source: National Immunization Program 2003 National Immunization Survey
[22] Source: Morbidity and Mortality Weekly Report 2003, Vol. 52 RR8

Healthcareworkers[23], and encourages professional health care organizations and institutions to follow them.

Prior to this influenza season, Chiron felt that substantial and innovative efforts were required to raise influenza immunization coverage rates in the groups for whom influenza immunization was recommended.[24] The events of this season only serve to magnify the need for such efforts. Even greater efforts will be required once the current challenges have been addressed and we return to a normal supply situation. One of the consequences of the shortage of influenza vaccine this season has been a significant shift in the emphasis of communication activities. This season, communication efforts on influenza have shifted away from a focus on encouraging influenza immunization to communicating the steps necessary to deal with the shortage. Since October 5, messaging has been focused on communicating the priority groups that should receive vaccine, asking others to step aside and highlighting respiratory hygiene and other preventative measures. Essentially, as a result of the shortage, many of the individuals who would normally be encouraged to *roll up their sleeves* and seek immunization are being asked to *roll down their sleeves* this year. If the supply situation returns to normal next season significant efforts will be needed to ensure those who properly stepped aside this season return and get immunized. In addition, renewed efforts will be needed to encourage those who never got vaccinated to seek immunization.

As the U.S. influenza supply is stabilized and diversified, there are key public health issues that need to be addressed:

- Raising awareness of the immunization recommendations among the medical community and general population.
- Dispelling some of the myths about influenza vaccine that exist, e.g. *"I can get influenza from the vaccine."*
- Encouraging immunization by highlighting the benefits of immunization and developing innovative programs for facilitating access to the vaccine.
- Extending the immunization season into December to increase the window in which vaccine could be supplied to the market.

The success that public-private partnerships have had in facing the challenges of this influenza season has served to reinforce Chiron's belief that collaboration between the public and private sector is the best means of increasing coverage rates. Comprehensive efforts need to be continued persistently and consistently over the next few seasons. Going forward sharpening the focus on the objective of the Healthy People 2010 goals of 90 percent coverage rates of non-institutionalized adults 65 years of age and older and 60 percent coverage rates of high-risk non-institutionalized adults 18-64 years of age is of critical importance[25]. The National Influenza Vaccine Summit, organized by the

[23] http://www.nfid.org/publications/hcwmonograph.pdf
[24] Statements to Government Reform Committee February 12, 2004 and to Senate Committee on Aging September 28, 2004.
[25] The target rate for institutionalized adults aged 18 and older is 90 percent.

American Medical Association in collaboration with the CDC, which brings together key stakeholders in the public and private sectors is a vehicle that has worked to help face the challenges of this season and is well placed to lead the efforts to raise coverage rates once influenza vaccine supply returns to normal levels.

Pandemic Preparedness

An influenza pandemic occurs when there is a major change (shift) in the influenza virus such that the majority of the world's population has not been previously exposed to the strain and is therefore extremely vulnerable to the virus. Influenza pandemic is a major public health threat with the potential to cause a rapid increase in morbidity and mortality. Three pandemics have occurred in the 20th century, the first in 1918. It is estimated that approximately 500,000 deaths due to influenza occurred in the United States between September 1918 and April 1919 and that the pandemic caused 20 million deaths worldwide. The 1918–1919 pandemic was the worst pandemic recorded, and mortality in more recent pandemics has been lower. The Asian influenza pandemic of 1957 is estimated to have caused approximately seventy thousands deaths in the United States, while the Hong Kong influenza pandemic of 1968 is estimated to have caused 33,000 deaths.

The use of antiviral drugs, public health measures such as quarantine and immunization of individuals with a pandemic strain-specific vaccine are likely to be important public health interventions for preventing the spread of disease and limiting the morbidity and mortality from pandemic influenza. The lessons learned this season in implementation of a prioritization scheme and in allocation and distribution of a limited amount of vaccine will be extremely useful in developing plans for vaccine distribution and allocation in the event of a pandemic.

The supply challenges experienced this season provide a preview of some of the challenges that will be faced in the event of a pandemic. The cycle time for production of influenza vaccine means that there will be a six-month lag between the isolation of the pandemic strain (followed by a decision to produce a vaccine against the strain) and the actual availability of the vaccine. In addition, quantities of vaccine will initially be limited. Therefore, there will be similarities to the current influenza season as the public health community will be faced with the allocation of a scarce commodity in order to ensure that it provides maximum benefit to the United States. Thus, it seems important that the following issues are resolved prior to the onset of a pandemic:

- Development of a prioritization scheme identifying who should receive priority in getting the vaccine.
- Determination of responsibility for decisions on vaccine allocation
- Identification for mechanisms for distribution of vaccine. For example, will it be the current system, a completely new primarily public sector system or a hybrid?

Resolution of these challenges in advance of a pandemic should occur as otherwise pandemic response might be hindered. There are parallels between the experience of this season and the pandemic situation. Therefore the lessons learned in handling the challenges currently faced may assist in the formulation of pandemic strategy.

A plan for allocation and distribution of vaccine in the event of a pandemic is of no value without the availability of a vaccine to distribute. It is therefore crucial for steps to be taken to ensure a pandemic vaccine can be developed as quickly as possible in the event of an influenza pandemic. Therefore, the world is fortunate that the National Institute of Allergy and Infectious Diseases (NIAID) has had the foresight as part of the NIAID Influenza Pandemic Preparedness Plan to support the manufacture and production of a candidate vaccine against potential pandemic strains of avian influenza. Chiron is participating in these efforts and believes partnerships between industry and governments are crucial to ensure the availability to the public of safe and effective vaccines against avian influenza as soon as possible. The need for additional investments should be evaluated once the results of these trials are available.

It is important to note that the current regulatory approval process would have to be expedited in order for manufacturers to rapidly convert to producing a monovalent pandemic vaccine in a timely fashion. Under the present system, obtaining regulatory approval could be a bottleneck in supplying pandemic vaccine. Discussions and planning should occur now between manufacturers and the FDA in order to determine the regulatory pathway for approval of a vaccine, including any amendments to official release requirements in the event of a pandemic. This would be of significant value to expedite the availability of supply should the pandemic occur.

From the perspective of an influenza vaccine producer, planning for a pandemic represents a significant challenge due to the nature of influenza vaccine production. Essentially, the following factors limit the ability to rapidly expand supply in the face of a pandemic under current circumstances:

- **Production capacity**—Influenza vaccine production capacity is aligned with annual demand for vaccine under normal circumstances, i.e., between pandemics, and therefore little or no surge capacity exists to meet pandemic demand.
- **Inability to stockpile**—Stockpiling of vaccine in preparation for a pandemic is not a viable strategy, as it is not possible to predict the strain that will cause the pandemic.
- **Supply of primary production material**—Currently, vaccines are produced using eggs, and ensuring an adequate supply of eggs to significantly increase production during a pandemic represents a significant challenge.
- **Specialized production facilities**—Additional quantities of vaccine could not be readily produced in facilities used for other vaccines, as production and purification equipment and facilities are specifically designed for influenza vaccines.

Looking forward, in the event of a pandemic, Chiron will strive to fulfill its responsibility to supply vaccine to the United States and international markets. To increase vaccine production, Chiron would undertake year-round production of a monovalent vaccine. Influenza vaccine production would be run continuously over the whole year as opposed to the current seasonal production cycle. However, it should be noted that this assumes that additional egg supply will be available to keep the facilities running year round. A monovalent vaccine containing the pandemic strain only would be produced as opposed to the standard trivalent vaccine containing three strains. Manufacturing capacity would therefore be increased by a factor of three, assuming that the vaccine contains the same amount of antigen as the conventional influenza vaccine.[26] Any increase in the antigen content of the pandemic vaccine would result in a proportional reduction in the number of doses that could be produced. As mentioned previously, the clinical data available to support the definition of the pandemic vaccine will be increased significantly by the trials planned by the NIAID.

Chiron estimates that implementing these two steps in the event of a pandemic would more than triple its influenza vaccine manufacturing capacity, assuming the pandemic vaccine contains the same amount of antigen as the normal vaccine. By the end of the decade, under its current plan, Chiron anticipates being able to increase its pandemic vaccine production by an additional 50 percent due to expanded production capacity in Liverpool and the availability of a cell-culture facility in Marburg.

In the face of a potential influenza pandemic, switching production to a monovalent pandemic vaccine imposes a significant financial risk. If the predicted pandemic failed to materialize, there would be no demand for the monovalent vaccine, and Chiron would be forced to destroy the vaccine. Therefore Chiron would be unlikely to make the decision to switch production from trivalent vaccine to a monovalent pandemic strain without a guarantee of mitigation of the downside risks it would face in the event of the pandemic not materializing. Further, Chiron would be unable to assume this risk without financial guarantees being in place due to the severe consequences of losing an entire year's revenues generated from the production of influenza vaccine. Therefore, in order to trigger a switch to pandemic vaccine production as quickly as possible in the event of a potential pandemic, governmental contract authority to purchase pandemic vaccine production by an agreed-upon mechanism of compensation should be in place prior to a pandemic. Such a contractual agreement between vaccine manufacturers and the government implies a limited role for the private sector in the marketing of a vaccine in the event of a pandemic. National governments would procure the vaccine, be responsible for its distribution and determine the priority of immunization. The events of this season have served to reinforce Chiron's belief that, in the event of a pandemic, the Department of Health & Human Services (HHS) will play a significant and crucial role in prioritization, allocation and distribution of the vaccines, even if the latter occurs through private sector channels.

[26] It should be noted that studies of experimental vaccines produced in response to the avian influenza A outbreaks in Hong Kong suggest that a greater dosage or an adjuvanted vaccine may be required. Therefore, whether this assumption will turn out to be valid is open to question.

Chiron recommends that a mechanism for indemnifying manufacturers, similar to that for smallpox and swine flu, be established in advance of a pandemic situation. The U. S. Government must address the considerable liability issues that manufacturers will face in a pandemic manufacturing situation. Under section 304 of the Homeland Security Act of 2002, "covered persons," including manufacturers, are deemed to be Public Health Service employees, so that the United States is the exclusively liable party under the FTCA for any injury or death arising out of the administration of a "covered countermeasure" against smallpox during an "effective period" defined by HHS declaration.[27] It is vital that Congress enact a similar provision for manufacturers producing influenza pandemic vaccines. Chiron welcomes the fact that section 890 of the American Jobs Creation Act of 2004, signed by President Bush on October 22, 2004, added trivalent influenza vaccine to the list of taxable vaccines included in the National Vaccine Injury Compensation Program.[28] However, in the context of this issue, it is important to note that coverage of a pandemic vaccine under this mechanism would be inappropriate due to concerns about the financial security of the fund as well as the very nature of a pandemic situation with regard to the volume of vaccine that would be administered in a pandemic situation.

Despite a potential increase in the supply of vaccine by a factor of greater than three, there still will be a global shortage of influenza vaccine in the event of a pandemic. Demand for influenza vaccine would increase dramatically compared to normal circumstances due to the need to immunize most of the global population and a potential increase in the number of doses required per person to provide immune protection from one to two. Current global influenza vaccine production capacity, estimated at roughly 300 million doses in a typical year,[29] will most likely be unable to cope with global demand, and therefore a shortage of vaccine is expected to occur.

Chiron is committed to maintaining supply to the United States in the event of a pandemic. However, the current location of Chiron's influenza manufacturing facilities outside of the United States imposes constraints on its ability to ensure this occurs, as it is not clear how global allocation of the vaccine will take place in the event of a pandemic. Where demand outstrips supply, it is possible that national authorities will impose constraints on the allocation of influenza vaccine by manufacturers under their jurisdiction. One of the constraints that may be imposed by national authorities is that producers be required to give priority to meeting national demand before shipping vaccine supply to traditional markets. For example, Chiron could be asked to give precedence to the United Kingdom in allocating vaccine supply from its Liverpool facility, as it is the only domestic source of supply for that country. Furthermore, once the needs of the United Kingdom were met, priority might be given to other European countries before allowing vaccine to be made available to the rest of the world. In addition, manufacturers with facilities located in European Union countries may be required by their national authorities to give precedence to the needs of other EU member countries-once domestic needs have been met-before vaccine can be exported outside of

[27] *See* 42 U.S.C. § 233(p)(1)-(2), (7).
[28] *See* H.R.4520 sec 890.
[29] Chiron internal estimate.

the EU, particularly for those member states that do no not have domestic production capacity. These variables are real and uncharted. Chiron believes it is important for the United States, United Kingdom and EU authorities to engage in discussions on pandemic influenza vaccine supply in advance of an outbreak in order to clarify supply priorities for its Liverpool facility. Chiron would welcome the opportunity to participate in these discussions.

An influenza pandemic will represent a significant challenge to Chiron, as it will need to rapidly expand influenza vaccine production at the expense of other products in its portfolio. Recognizing this challenge, Chiron is committed to supporting global pandemic preparedness efforts prior to (and during) the inevitable occurrence of a pandemic. Chiron believes that the lessons learned from handling this season's shortage can be extremely useful particularly with respect to policies for prioritization, allocation and distribution of pandemic vaccine. In addition, Chiron believes that the strategic public education programs that it considers crucial to increase demand for influenza vaccine during interpandemic years to assure a sustainable and uninterrupted supply of influenza vaccines will benefit U.S. pandemic preparedness. A strong, preferably domestic, influenza vaccine manufacturing base will ensure that the United States has an adequate supply of vaccine in the event of a pandemic. In addition, raising coverage rates will enhance the ability of the public health system to cope with the challenge of administering large amounts of vaccine to the population over a relatively short time frame. The annual influenza campaign provides a means of testing the preparedness and improving the capacity of our infrastructure to deliver and administer vaccine in the event of a pandemic or other bioterror threat.

Conclusions

The challenges of this season and the way they are being addressed have reinforced Chiron's belief that going forward significant efforts are required to raise immunization coverage rates and that public partnerships are the best way to accomplish this goal. Raising demand is a key element to creating a sustainable market for influenza vaccine, critical for ensuring an uninterrupted supply of influenza vaccine from a diversified manufacturing base over the long-term. This is an essential component in helping position the United States for preparedness for a global influenza pandemic by helping assure a supply of vaccine. If the lessons learned from coping with shortages of vaccine this season are applied the challenges of this season may offer a significant long term benefit by strengthening the ability of the United States to deal with the annual influenza epidemic and a potential pandemic.

Thank you for the opportunity to present the views of Chiron Corporation. I am happy to answer any questions you may have for me.

Chairman TOM DAVIS. Dr. Coelingh, thank you for being with us.

Ms. COELINGH. Good afternoon. My name is Dr. Kathleen Coelingh, and I am the senior director of regulatory and scientific affairs and MedImmune, a Maryland-based vaccine company that manufactures the innovative intranasal influenza vaccine, FluMist. Approved by the FDA last year for healthy persons 5 to 49 years of age, FluMist is the first advancement in influenza prevention in 50 years.

We are at a critical juncture in defining what the influenza vaccine market will look like in the future and how U.S.-based vaccine manufacturers will meet the needs of this country going forward. What will be the incentives for companies to build U.S.-based manufacturing facilities? How will our government drive vaccine acceptance, utilization, and demand, since it is demand that ultimately determines the supply of vaccine manufactured? And what will be the incentive for continued innovation?

MedImmune recommends that this committee support and encourage two key longer term solutions in the realm of policy changes and incentives for innovation. The first recommendation is to move toward adoption of a universal recommendation for influenza vaccine for all Americans. The current recommendations, which are based on age groups and an ever-expanding list of underlying chronic medical conditions are both complicated for the health care provider to follow and are confusing to the public. We believe that a universal recommendation will stabilize demand for vaccine, thereby leading to increased vaccine supply and ultimately to substantially lowering the current morbidity and mortality due to influenza.

As an interim step, MedImmune recommends required vaccination of school-aged children, who have a very high influenza attack rate and spread influenza to younger siblings, their parents, and their grandparents. Thus, vaccination of school children would directly benefit not only the children themselves, but may also have the potential to greatly reduce the impact of influenza in our communities. This concept of protecting an entire community by vaccinating the school-aged children has already been demonstrated in Japan and in studies in the United States. In conjunction with this interim step, money must be appropriated to expand the education of the public and the medical community about the seriousness of influenza and the value of influenza prevention.

The second solution that MedImmune recommends to ensure continued influenza vaccine supply is to provide tax incentives for scientific innovation and for construction of U.S.-based facilities. MedImmune is a primary innovator in the area of molecular techniques, termed "reverse genetics." The use of reverse genetics is vital to producing seeds for an H5N1 pandemic vaccine, as we heard from Dr. Fauci earlier. MedImmune owns multiple patents in this area and has granted free access to its reverse genetics intellectual property not only to governmental organizations, but also to other companies who are developing pandemic influenza vaccines. MedImmune is currently collaborating with the National Institutes of Health to produce intranasal pandemic vaccines and to test them in clinical trials.

MedImmune also has core expertise in the innovative area of cell culture manufacturing. The main advantages of manufacturing using cell culture are elimination of our dependence upon egg supplies and more consistent and rapid production, which will be critical in the event that the egg supply is decimated by the emergence of a pandemic virus. The transition from egg-based to cell-based manufacturing will require considerable investment in the construction of new facilities and potentially additional clinical studies. Tax incentives to subsidize the cost of such innovations are necessary to guarantee a more stable vaccine supply on a yearly basis and when the pandemic comes.

The government also needs to incentivize manufacturers to build manufacturing facilities within the United States. There is an increased risk that, with offshore manufacturing, companies will face political decisions that may prevent vaccine products from entering the United States, particularly in the event of a catastrophic pandemic. Tax incentives for U.S.-based manufacturing facilities would encourage manufacturers to build more facilities in the United States.

To address what MedImmune has done during the current vaccine shortage, since October 5th, we have worked diligently with the appropriate authorities to, first, blend and fill our excess bulk vaccine to produce an additional 2 million doses of FluMist, bringing our total production for this year to 3 million doses; second, we have supplied the Department of Defense with up to 400,000 doses, the CDC with 125,000 doses, and we have supplied hospitals with over 60,000 free doses of FluMist this year; third, we have supplied the FDA with new storage data for FluMist, which they have promptly reviewed and approved, allowing the additional 2 million doses of FluMist to be stored in a household freezer without the requirement for the special freezer box; and, finally, we have worked closely with the CDC and the Advisory Committee on Immunization Practices to clarify that FluMist is an option for all healthy people 5 to 49 years of age who want to consider protecting themselves from influenza this season.

Shifting gears a bit and looking forward to next season, you must understand that the influenza vaccine manufacturing campaign for the 2005–2006 season is starting right now. We are already preparing the new vaccine seeds that we anticipate will be in the next year's vaccine, and we are making decisions about how many doses of vaccine we will manufacture, including deciding how many chicken eggs to order. Thus, the amount of FluMist that will be available next season will soon be fixed.

With some additional regulatory cooperation, MedImmune has the capacity to produce between 8 to 10 million doses for next season. These regulatory actions include: FDA approval allowing for the production of larger lot sizes and filtration; acceptance by the FDA of our application to permanently eliminate the requirement for the FluMist storage box; and, finally, FDA acceptance of recently sumitted data that supports the expansion of the FluMist indication to include the 30 million healthy Americans who are 50 to 64 years old, a group that is not eligible for the injectable flu shot this season, and may not be eligible again next season, should we experience a continuing shortage.

In summary, MedImmune is clearly at a crossroads in determining not only how much FluMist will be available next season, but also whether our investments and innovation will be recouped in this market. Our level of production for next season depends on the occurrence of several immediate regulatory actions. But whether MedImmune expands its production and whether companies continue their efforts to develop influenza vaccines depends in large part upon the government's commitment to encouraging innovation and driving demand. Requiring childhood influenza vaccination as an interim step toward a universal recommendation and legislating tax incentives for both scientific innovation and U.S.-based manufacturing will go a long way to ensuring an adequate supply of influenza vaccine in the near future.

Thank you.

[The prepared statement of Ms. Coelingh follows:]

MedImmune, Inc. Testimony

November 17, 2004

Government Reform Committee

Good morning. My name is Dr. Kathleen Coelingh, and I am the Senior Director of Regulatory and Scientific Affairs at MedImmune, Inc, a Maryland-based biotechnology company that manufactures the innovative intranasal influenza vaccine, FluMist. Approved by the FDA last year for healthy persons 5 to 49 years of age, FluMist is the first advancement in influenza prevention in 50 years.

We are at a critical juncture in defining what the influenza vaccine market will look like in the future and how U.S. based vaccine manufacturers will meet the needs of this country going forward. What will be the incentives for companies to build U.S. based manufacturing facilities? How will our government drive vaccine acceptance, utilization, and demand – since it is demand that ultimately determines the supply of vaccine manufactured? And what will be the incentive for continued innovation?

MedImmune recommends that this committee support and encourage two key longer-term solutions in the realm of policy changes and incentives for innovation. The first recommendation is to move towards adoption of a universal recommendation for influenza vaccine for all Americans. The

current recommendations, which are based on age groups and an ever-expanding list of underlying chronic medical conditions, are both complicated for the health care provider and confusing to the public. We believe that a universal recommendation will stabilize demand for vaccine, thereby leading to increased vaccine supply, and ultimately to substantially lowering the current morbidity and mortality rates.

As an interim step, MedImmune recommends required vaccination of school-aged children, who have a very high influenza attack rate and spread influenza to younger siblings, parents, grandparents, etc. Thus, vaccination of school children would directly benefit the children themselves and may also have the potential to greatly reduce the impact of influenza in our communities. This concept of protecting an entire community by vaccinating the school-aged children has been demonstrated in Japan and in studies in the U.S. In conjunction with this interim step, money must be appropriated to expand the education of the public and the medical community about the seriousness of influenza and the value of influenza prevention.

The second solution that MedImmune recommends to ensure continued influenza vaccine supply is to provide tax incentives for scientific innovation and for construction of U.S. based facilities. MedImmune is a primary innovator in the area of molecular techniques, termed "reverse genetics." The use of reverse genetics is vital to producing seeds for an H5N1 pandemic vaccine. MedImmune owns multiple patents in this area and has granted free access to its reverse genetics intellectual property to government organizations and to other companies developing pandemic influenza vaccines. MedImmune is currently collaborating with the National Institutes of Health to produce intranasal pandemic vaccines and to test them in clinical trials.

MedImmune also has core expertise in the innovative area of cell culture manufacturing. The main advantages of manufacturing using cell culture are elimination of dependence on egg supplies and more consistent and rapid production, which will be critical in the event that the egg supply is decimated by the emergence of a pandemic virus. The transition from egg-based to cell-based manufacturing will require considerable investment in the construction of new manufacturing facilities and clinical studies. Tax incentives to subsidize the cost of such innovations are necessary to

guarantee a more stable vaccine supply on a yearly basis and when the pandemic arrives.

The government also needs to incentivize manufacturers to build manufacturing facilities in the U.S. There is an increased risk that with offshore manufacturing, companies will face political decisions that may prevent product from entering the U.S. – particularly in the event of a catastrophic pandemic. Tax incentives for U.S.-based manufacturing facilities would encourage manufacturers to build more facilities in the U.S.

To address what MedImmune has done during the current vaccine shortage, since October 5th, we have worked diligently with the appropriate authorities to:

1) Blend and fill our excess bulk vaccine to produce an additional 2 million doses of FluMist, bringing total production this year to about 3 million doses;
2) Supply the Department of Defense with 400,000 doses, the CDC with 125,000 doses, and hospitals with over 40,000 free doses and more than 200,000 commercially purchased doses.

3) Supply the FDA with new storage data for FluMist, which they promptly reviewed and approved, allowing the additional 2 million doses of FluMist to be stored in a household freezer without the requirement for a special freezer box; and
4) Work closely with CDC and ACIP to clarify that FluMist is an option for all healthy people from 5 to 49 years of age to consider if they want to protect themselves against the flu this season.

Shifting gears a bit and looking ahead to next season, you must understand that the influenza vaccine manufacturing campaign for the 2005-2006 season is starting right now. We are already preparing the new vaccine seeds for strains anticipated to be in next year's vaccine and making decisions about how many doses of vaccine we will manufacture next year, including deciding how many eggs to order. Thus, the amount of FluMist that will be available for next year will soon be fixed.

With some additional regulatory cooperation, MedImmune has the capacity to produce between 8 and 10 million doses next season. These regulatory actions include:

1) FDA approval allowing for the production of larger lot sizes and product filtration;

2) Acceptance by the FDA of our application to permanently eliminate the requirement for FluMist storage in special freezer boxes; and

3) FDA acceptance of recently submitted data that supports the expansion of the FluMist indication to include the 30 million Americans who are 50 to 64 years old, a group that is not eligible for the injectable flu shot this year, and may not be eligible again next year should we experience a continuing shortage.

To summarize, MedImmune is clearly at a crossroads in determining not only how much FluMist will be available next season, but also whether our investments in innovation will be recouped in this market. Our level of production for next season depends upon the occurrence of several immediate regulatory actions. But whether MedImmune expands its production and whether companies continue their efforts to develop influenza vaccines depends in large part upon the government's commitment to encouraging innovation and driving demand. Requiring childhood flu vaccinations as an interim step towards a universal recommendation and legislating tax incentives for both scientific innovation and U.S.-based

manufacturing will go a long way towards ensuring an adequate supply of influenza vaccine in the near future.

Thank you.

Chairman TOM DAVIS. Thank you for your testimony.

We will hear now from Dr. Robert Stroube, Virginia State health commissioner with the Association of State and Territorial Health Officials.

Welcome, sir, and you are recognized.

Dr. STROUBE. Thank you, Mr. Chairman.

Mr. Chairman, distinguished members of the House Government Reform Committee, my name is Robert Stroube. I am the health commissioner in Virginia. I am honored to be testifying before you today, and I would like to thank you for convening this hearing on this really crucial problem that we are facing.

The ongoing flu vaccine shortage continues to present many challenges for Virginia, as well as the other States. State and local health departments have been working nonstop since October 5th to address this issue.

As of today, Virginia Health Department has received a total of 159,565 doses of flu vaccine, which we have distributed to our local health departments and our long-term care facilities for administration to people at high-risk of complications from the flu. In addition, the Health Department has received 84,480 doses of flu vaccine intended for high-risk children who are eligible for the Vaccines for Children program. According to recent information from CDC, we are expecting another shipment of about 150,000 doses, which we will allocate to long-term care facilities, hospitals, and other health care facilities with unmet vaccine needs.

The Health Department is now providing the flu vaccine to many more people and providers than we would during a typical flu season. You might say that the Health Department is now the broker in the management of the flu vaccine to help ensure that the vaccine goes where it is most needed.

We applaud the reallocation efforts of CDC and of Aventis, and we are grateful for the timely receipt of the vaccine that we have. We firmly believe that as the public health agency for Virginia, it is our responsibility to guide allocation distribution of vaccine to those who are most in need.

However, we do want the committee to be aware of the immense workload this situation has placed on local and State Health Department personnel. During the first week of November, the State Health Department distributed more than 77,000 doses of vaccine to our 35 local health districts on a population-based formula. Each health district developed a flu vaccine distribution plan based on the needs of the high-risk persons in that community. In developing those plans, all the health districts had to make difficult decisions on how to distribute the limited amount of vaccine. In some areas they opened up phone lines and began taking appointments on first call-first served basis; some distributed the vaccine to health care providers in the community; some pre-identified high-risk individuals who were unable to get the vaccine in the private sector.

In Chesterfield County, just outside of Richmond, the health department there held a "drive through" flu clinic this past weekend so that high-risk people wouldn't have to stand in line out in the cold. That one clinic required 120 staff members to manage all of the logistics. The health director there estimates this ongoing issue

has required more than 600 hours of work from senior-level managers, supervisors, and other personnel. The health department's time devoted to this ongoing flu shortage supply issues means time away from other important public health practices.

Another example is our ongoing distribution of 82,000 doses of vaccine to long-term care facilities in Virginia who did not receive flu vaccine. In order to accurately determine which facilities still needed vaccine, all of our 35 health districts surveyed each facility in their community. The health department usually does not provide flu vaccine directly to long-term care facilities. Most of these facilities ordered vaccine this year through a distributor or directly from the manufacturer, and most ordered through Chiron Vaccines.

In our Immunization Program, we typically only need one full-time person working on the flu vaccine program. This year we have four staff persons working continuously managing the issue at the State level. In addition, the issue has required the involvement of all our senior-level management, our public information personnel, and some of our emergency preparedness personnel, which manage State level planning, logistics communication and coordination. We owe a tremendous amount of gratitude to our hardworking and dedicated public health employees who are spending hours planning and executing flu vaccine clinics or answering phone calls from our worried elderly and our other high-risk citizens. I would like to take this opportunity to personally thank each and every person for their service to our citizens.

At the beginning of the shortage, one of our biggest difficulties was determining how much flu vaccine was available in the private sector. We would like to thank CDC and Aventis for their efforts to make this information about vaccine distribution in the private sector available to us through our secure Web-based data base. This information has helped us to identify geographic gaps in vaccine supply and focus our distribution efforts to providers in those areas. This system is constantly being upgraded, and just this morning, before I left to come here, we found out that they have now upgraded it, so we will be ordering our vaccine directly and sending it through reallocation out over this data base.

Even with all the flu vaccine now coming to Virginia, we do not expect that we will have enough vaccine for every high-risk individual in Virginia this year. To help alleviate the situation, we continue to provide the public with useful tips for preventing the spread of flu in the absence of vaccine, such as frequent hand washing and staying home from work when sick. In addition, we have been encouraging the use of pneumococcal vaccine among the elderly and individuals with chronic medical conditions. This widely available vaccine can help prevent pneumonia, which in many cases is a secondary complication of flu.

We would like to thank CDC and the Department of Health and Human Services for all the work they have done to help manage the situation and secure flu vaccine for the State health departments. We believe that everyone involved at the Federal, State, and local level has done an outstanding job addressing the problem.

But I cannot stress enough how important it is for Congress to take steps now to prevent this flu vaccine shortage from occurring

again. This situation has required an enormous amount of time and effort to manage, and has had a major fiscal and human resource impact on other important public health activities.

Efforts must commence now at the national level to ensure a stable flu vaccine supply. As many of us have stated in previous testimony, the present system of vaccine production distribution is incapable of effectively and efficiently responding to the current demand for the flu vaccine. It is imperative that Congress take steps now to support the development of a more reliable and flexible vaccine production and distribution process. In addition, efforts need to be made now to guarantee an ample supply of flu vaccine from multiple manufacturers.

Given the estimated 36,000 people that die each year in the United States from the complications of flu and the threat of a flu pandemic, I believe addressing the flu vaccine production and distribution problem has to be of the highest priority for Congress.

Thank you.

[The prepared statement of Dr. Stroube follows:]

Statement of

ROBERT B. STROUBE, MD, MPH

STATE HEALTH COMMISSIONER
VIRGINIA DEPARTMENT OF HEALTH

Before the

COMMITTEE ON GOVERNMENT REFORM

of the

UNITED STATES HOUSE OF REPRESENTATIVES

Hearing on

U.S. INFLUENZA VACCINE SUPPLY

November 17, 2004

Mr. Chairman and distinguished members of the House Government Reform Committee, my name is Dr. Robert Stroube. I am the State Health Commissioner for the Virginia Department of Health (VDH), and I am honored to be testifying before you today. I would like to thank the Chair and the committee members for convening this hearing.

As State Health Commissioner I serve as the principal advisor to Virginia Governor Mark Warner, Virginia Secretary of Health and Human Resources Jane Woods and the Virginia General Assembly on a wide range of public health issues. I earned a Doctor of Medicine degree from the Medical College of Virginia, a Masters in Public Health from the Johns Hopkins University, and an undergraduate degree from the College of William and Mary. I am a specialist in preventive medicine and certified by the American Board of Preventive Medicine.

The ongoing flu vaccine shortage continues to present many challenges for Virginia. The Virginia Department of Health has been working non-stop to address this issue.

As of November 11, we have received a total of 159,565 doses of flu vaccine which has been distributed to local health departments and long-term care facilities for administration to people at high-risk of complications from the flu. In addition, the health department has received 84,480 doses of flu vaccine intended for high-risk children eligible for the Vaccines for Children Program. According to recent information from the U.S. Centers for Disease Control and Prevention (CDC), we can expect another

shipment of 150,000 doses for allocation to long-term care facilities, hospitals and other health care providers with unmet vaccine needs.

The health department is now providing the flu vaccine to many more people and providers than we would during a typical flu season. You might say that the health department is now the 'broker' in the management of the flu vaccine to help ensure that the vaccine goes where it is needed most.

We applaud the re-allocation efforts of the CDC and Aventis, and we are grateful for the timely receipt of vaccine. We firmly believe that as the public health agency for Virginia it is our responsibility to guide the allocation and distribution of vaccine to those most in need. However, we do want the committee to be aware of the immense work load this situation has placed on our state and local health department personnel.

During the first week of November, the state health department distributed more than 77,000 doses of vaccine to our 35 local health districts on a population based formula. Each health district developed a flu vaccine distribution plan based on the needs of the high-risk persons in their community. In developing those plans, all of the health districts had to make difficult decisions on how to distribute the limited amount of vaccine. In some areas they opened up the phone lines and began taking appointments on a first call-first served basis, some distributed the vaccine to other health care providers in their community, and some pre-identified high-risk individuals who are unable to get the vaccine in the private sector.

In Chesterfield County, just outside Richmond, the local health department held a "drive through" flu vaccine clinic this past weekend so that high-risk people would not have to stand in line out in the cold. That one clinic required 120 staff members to manage all of the logistics. The Chesterfield Health Director estimates that this ongoing issue has required more than 600 hours of work from senior-level managers, supervisors and other personnel. The local health department's time devoted to this ongoing flu vaccine shortage supply issues means time away from other important public health practices and in some cases may mean the health department is unable to forge as vigorous a response as usual to ongoing outbreaks of communicable disease.

Another example is our ongoing distribution of 82,000 doses of vaccine to long-term care facilities in Virginia who did not receive flu vaccine. In order to accurately determine which facilities still needed vaccine, all of our 35 local health districts surveyed each facility in their community. The health department usually does not provide flu vaccine directly to long-term care facilities. Most of these facilities order through a distributor or directly from the manufacture. This year most of the long-term care facility orders were placed for Chiron vaccine and now these facilities are relying on the health department for their vaccine.

In our Immunization Program we typically only need one full time person working on the flu vaccine program. This year we have four staff persons working continuously managing this issue at the state level. In addition, the issue has required the involvement of all of our senior-level management, public information personnel and some of our

emergency preparedness personnel to manage state level planning, logistics, communication and coordination.

We all owe a tremendous amount of gratitude to the hard working and dedicated public health employees who are spending hours planning and executing flu vaccination clinics or answering phone calls from our worried elderly and other high-risk citizens. I would like to take this opportunity to personally thank each and every person for their service to our citizens.

At the beginning of the shortage one of our biggest difficulties was determining how much flu vaccine was available in the private sector. We would like to thank the CDC and Aventis for their efforts to make information about vaccine distribution in the private sector available to us through a secure Web-based database. This information has helped us identify geographical gaps in vaccine supply and focus our distribution efforts to providers in those areas.

However, we are still unable to determine how many of those distributed vaccine doses actually still remain unused, if any. And even if we were able to identify unused vaccine in the private sector, we do not have legal authority to redirect it without a state declaration of emergency. The database also does not provide information regarding which providers or areas in Virginia are scheduled to receive a shipment of flu vaccine in the coming days. Even our own pharmacy did not know exactly when they would

receive our re-allocated shipment until the day it arrived. This has made it difficult to make decisions ahead of time regarding our flu vaccine distribution plans.

Even with all of the flu vaccine that is now coming into Virginia, we do not expect that we will have enough vaccine for every high-risk individual in Virginia this year. To help alleviate this situation, we continue to provide the public with useful tips for preventing the spread of flu in the absence of vaccine, such as frequent hand-washing and staying home from work when sick. In addition, we have been encouraging the use of the pneumococcal vaccine among the elderly and individuals with chronic medical conditions. The widely available vaccine can help prevent pneumonia, which in many cases is a secondary complication following infection with influenza.

We would like to thank the CDC and the U.S. Department of Health and Human Services for all the work they have done to help manage this situation and secure flu vaccine for the state health departments. We believe that everyone involved at the federal, state and local level has done an outstanding job addressing the problem.

But I cannot stress enough how important it is for Congress to take steps now to prevent this flu vaccine shortage from occurring again. This situation has required an enormous amount of time and effort to manage and has had a major fiscal and human resource impact on other important public health activities.

Efforts must commence now at the national level to ensure a stable flu vaccine supply. As many of us have stated in previous testimony, the present system of vaccine production and distribution is incapable of effectively and efficiently responding to the current demand for flu vaccine. In the event we experience a large scale flu outbreak or pandemic the situation will be much worse. It is imperative that Congress take steps now to support the research development of a more reliable and flexible vaccine production and distribution process. In addition, efforts need to be made now to guarantee an ample supply of flu vaccine from multiple manufactures.

Given the estimated 36,000 people that die each year in the U.S. from the complications of influenza and the threat of a flu pandemic, I believe addressing the flu vaccine production and distribution problem must be of the highest priority for Congress.

Thank you for this opportunity to speak with you today. I would be pleased to answer any questions you may have.

Chairman TOM DAVIS. Dr. Klein, thanks for being with us.

Dr. KLEIN. Thank you very much, Mr. Chairman. I am Jerome Klein, a pediatrician, a professor for pediatrics at Boston University, and a member of the National Vaccine Advisory Committee.

A robust domestic vaccine capability is a necessity not only for old threats such as influenza, but for new and virulent microorganisms spread by natural means or by bioterrorist activity. The current shortage of influenza vaccine underlines the vulnerability of the supply of all recommended vaccines in the United States, and I would like to touch on four areas that have already been discussed in part in the prior discussions: first, the loss of vaccine manufacturing capability in the United States; second, the issue of stockpiling; three, Food and Drug Administration regulatory practices; and, fourth, the liability concern.

First, the loss of manufacturing capability. Vaccine manufacturing is complex, involves uncertainties that do not exist in pharmaceutical drug manufacturing. There is no question that additional influenza vaccine manufacturers this year, if available, would have diminished the effect of loss of the Chiron product. Companies leave the marketplace when a product no longer provides a reasonable return on investment. Appropriate incentives must exist that encourage companies to enter and remain in the vaccine business. What is needed now is a sustained effort to provide concrete proposals that will have a durable effect. A multi-disciplinary group to include all stakeholders should be convened to evaluate and propose appropriate incentives for manufacturers to ensure supply of existing vaccines and stimulate development of new vaccines, and that is the encouragement of domestic vaccine producers, not seeking vaccine overseas.

Second, the issue of strengthening vaccine stockpiles. A program to stockpile vaccines has been available since the 1980's. The principle is simple: government purchase of vaccine provides a repository that can be called on if there is an emergent need. Subsequent to the 2002 workshop held by National Vaccine Advisory Committee, there was additional funding that was provided to expand the stockpile program. However, no new vaccine has been added because of a Securities and Exchange Commission accounting regulation that bars vaccine manufacturers from claiming sales to the stockpile program as revenue until they come out of the stockpile. This impediment to a universally approved response to enhance vaccine supply should be remedied as soon as possible, because a new influenza vaccine is prepared each year and the stockpile concept is not applicable. A redundancy of supply has been suggested. The government purchase program would be expanded so that additional vaccine beyond that required for patients at risk would be instituted. Since influenza immunization would be a value for healthy children and adults, the additional vaccine would not be wasted.

Three, streamlining the regulatory activity of the Food and Drug Administration. The current good manufacturing practices need to be dynamic, with changes to maintain or improve facilities to current standards, but allow sufficient flexibility to ensure continued vaccine production. In addition, a review of current GMP and regulation should be instituted to consider whether the complexity of

manufacturer of vaccines and biologics warrants a separate and different mode of regulation than that used for drugs, which is the practice currently.

Finally, the liability issue, which, as I understand it has little role in the current concern about the contamination issue at the Chiron facility. But there is renewed concern about litigation associated with the manufacture and administration of vaccines. The National Childhood Vaccine Injury Compensation Program was established in 1986 to compensate quickly and appropriately individuals who suffered serious injuries associated with the administration of an FDA-approved vaccine. The program removed the threat of liability from the manufacturer, as well as those who administer vaccines, and successfully stabilize the market. The VICP should be maintained and strengthened to include additional vaccines. When those additional vaccines are added, additional staff will be needed. So the VICP program needs to be supported. Strengthening the VICP would benefit manufacturers, providers, consumers, and further safeguard the Nation's vaccine supply.

The development of safe and effective vaccines during the past 50 years, since the introduction of the polio vaccine, has been one of the great success stories of American medicine. However, there is concern, as has been discussed today, that future contributions of the vaccine industry may be jeopardized by lack of attention to basic issues. Solutions are not easy to come by in a sustained effort. The collaboration of all stakeholders and political will will be required.

Thank you very much.

[The prepared statement of Dr. Klein follows:]

Second Hearing on US Influenza Vaccine Supply - November 17, 2004
House of Representatives - Committee on Government Reform

Vulnerability of Vaccine Supply
Jerome O. Klein, MD
Professor of Pediatrics Boston University School of Medicine

I appreciate the opportunity to address the Committee about the current shortage of influenza vaccine and the vulnerability of vaccine supply in the United States. The development and introduction of vaccines in the past 50 years has been an extraordinary success story: polio and measles are virtually eradicated; a new vaccine for prevention of pneumococcal diseases has reduced the incidence of meningitis and protected unimmunized adult contacts; rotavirus vaccines in clinical trials are likely to reduce death due to diarrhea in hundreds of thousands of infants. Vaccines are a national resource and their efficacy can be measured not only in decreased death and disability but also in direct economic benefits. A thriving vaccine industry is a necessary antidote to the threat of new and virulent microorganisms by natural means or bioterrorist activity. An influenza pandemic will occur in the near future; the question is when not whether it will occur. Our major defense against hundreds of thousands of deaths and economic chaos that are the possible results of pandemic influenza is an effective vaccine that could be manufactured and distributed quickly in advance of the arrival of the virus. We are fortunate that a project to identify the genomes of various human and avian influenza viruses that would be invaluable in rapid development of an effective vaccine to thwart a pandemic is underway at the National Institutes of Health. But there are problems in vaccine supply that need to be addressed now.

The current shortage of influenza vaccine underlines the vulnerability of the supply of recommended vaccines in the United States. Vaccine shortages have occurred in the past, are a current concern, and are likely to occur in the future. In 2001, 8 of the 11 recommended childhood vaccines were in short supply. The steps needed to maintain the supply of current vaccines and encourage the introduction of new vaccines were discussed at a workshop held in February 2002 under the auspices of the National Vaccine Advisory Committee. Some of the concerns raised at the workshop have been addressed but there is need for additional and sustained effort to achieve appropriate resolution. Among the issues addressed at the workshop (which are pertinent to the current influenza vaccine shortage) were: 1. Increasing valuation of vaccines; designing appropriate financial incentives to assure the manufacture and distribution of available vaccines and stimulate the development and testing of new vaccines; 2. Encouraging the efficient use of vaccine stockpiles; 3. Streamlining the regulatory processes and activities of the Food and Drug Administration so vaccines are appropriately monitored but without a negative impact on vaccine supply; and 4. Reducing liability associated with the manufacture and administration of FDA approved vaccines by strengthening the Vaccine Injury Compensation Program.

Increasing Financial Incentives

Vaccine manufacturing is complex and involves uncertainties that do not exist in pharmaceutical drug manufacturing. Influenza vaccines pose unique problems, since the

composition change almost every year, the yield of candidate strains may not be as high as desired which results in fewer doses, or strains may take additional time to obtain optimal yields, resulting in delays in the availability of vaccine. Today there are only 6 vaccine manufacturers in the United States; in the 1970s there were 26 manufacturers. Many important vaccines have only one US manufacturer (eg. measles, mumps, rubella vaccine, the chicken pox vaccine, inactivated polio vaccine and pneumococcal vaccines); when there is a failure in production of the single manufacturer the shortage is immediate and acute. Even when there are three manufacturers, such as with the influenza vaccines, loss of the product of one manufacturer leads to substantial decrease in supply. Additional influenza vaccine manufacturers would have diminished the effect of loss of the Chiron vaccine.

Companies leave the marketplace when a product no longer provides a reasonable return on investment. Appropriate incentives must exist that encourage companies to enter and remain in the vaccine business. Incentives for research, development and production to provide a fair return on capital may be made available by means other than increased price. Such incentives could include tax relief for new facilities or reconstruction of old facilities or other forms of subsidy as well as guaranteed market and price. The financing of vaccines to assure access and availability is complex. The Institute of Medicine recently published an extensive review and made innovative suggestions for vaccine finance (Financing Vaccines in the 21st Century: Assuring Access and Availability; National Academies Press, Washington DC. 2004). The NVAC followed up the IOM report with further recommendations (www.hhs.gov/nvpo). What is needed now is a sustained effort to provide concrete proposals that will have durable effect; a multi-disciplinary group to include all the stakeholders should be convened to evaluate the nature of appropriate incentives for manufacturers to assure the supply of existing vaccines and stimulate development of new vaccines.

Strengthening Vaccine Stockpiles

We need to support stockpiling vaccines to maintain supply for shortages of vaccines approved for universal immunization. A program to stockpile vaccines has been available since the 1980s. The principle is simple; government purchase of vaccines provides a repository that can be called on if there is an emergent need. Under usual circumstances, the vaccine can be rotated out of the stockpile before the expiration date so that vaccine is not wasted. As a result of recent legislation funding was made available to expand the stockpile program. However, no new vaccine has been added because of a Securities and Exchange Commission accounting regulation that bars vaccine manufacturers from claiming sales to the stockpile program as revenue until they come out of the stockpile. The SEC "bill and hold guidance" is designed to protect investors by preventing companies from counting a sale as revenue until the buyer takes delivery or in the case of vaccines, is delivered from the stockpile. As a result of the SEC regulation vaccine manufacturers have resisted enrolling in the stockpile program because the moneys from products sold can't be counted as revenue until they come out of the stockpile. This impediment to a universally approved response to vaccine supply issues should be remedied as soon as possible. Because a new influenza vaccine is prepared each year, the stockpile concept is not applicable. Rather a redundancy of supply has been suggested; the government purchase program would be expanded so that additional vaccine, beyond that required for patients at risk, would be instituted. Since influenza immunization would be of value for healthy children and

adults, the additional vaccine would not be wasted.

Streamlining the Regulatory Activity of the FDA

The FDA has regulatory authority to assure that vaccines are safe and effective. The role of the FDA in the current influenza shortage is under investigation but there are general issues that need to be addressed. Through current Good Manufacturing Practices (cGMP), the FDA maintains oversight of manufacturing plants. The implementation of cGMP should be reviewed on a continuing basis so that the regulations do not have a negative impact on vaccine supply except when needed to ensure vaccine safety. The current Good Manufacturing Practices need to be dynamic with changes that incorporate technological advances and maintain or improve facilities to current standards but allow sufficient flexibility to ensure continued vaccine production within the context of maintaining safety and effectiveness. A review of cGMP and regulations should be instituted to consider whether the complexity of manufacture of vaccines and biologics warrants a separate and different mode of regulation than that used for drugs.

Responding to Liability Issues

The question of liability has been raised as a factor contributing to the influenza vaccine shortage. Although the current shortage is due to contamination in the manufacture of the Chiron vaccine, there is renewed concern about litigation associated with the manufacture and administration of vaccines. The National Childhood Vaccine Injury Compensation Program (VICP) was established in 1986 to compensate quickly and appropriately individuals who suffered serious injuries associated with administration of an FDA approved vaccine. The VICP was designed to compensate individuals who suffered a serious adverse event as a result of administration of a covered vaccine in a manner that was rapid, generous and appropriate. Prior to its enactment, litigation led to national shortages, withdrawal of manufacturers from the marketplace, and instability of supply of essential childhood vaccines. The program removed the threat of liability from the manufacturer as well as those who administer vaccines and successfully stabilized the market. The VICP should be maintained and strengthened as supported by scientific evidence to include additional vaccines. Additional staff is necessary to assure prompt review of claims. Strengthening the VICP would benefit manufacturers, providers and consumers and further safeguard the nation's vaccine supply.

Summary and Conclusions

The current shortage of influenza vaccine provides an opportunity to review the vulnerability of vaccine supply. The immediate problem is concern for oversight of manufacture at the Chiron vaccine facility. But many of the issues of vaccine supply are complex and will required sustained effort and political will.

A multi-disciplinary group should be convened to identify appropriate incentives for manufacturers to sustain the supply of existing vaccines and stimulate development of new vaccines.

Funds should be increased for vaccine stockpiles to include all routinely administered vaccines in sufficient quantity to be used for acute shortages or surge demands; a redundancy in supply of influenza vaccine would be valuable in alleviating any shortages associated with the annual manufacture. The current impasse in executing the expanded stockpile program due to the SEC regulation of "Bill and Hold Guidance" was not meant for vaccine stockpiles and should be resolved at the earliest possible time.

The regulatory processes and activities of the FDA need to be streamlined and strengthened by review of the implementation of current Good Manufacturing Practices to assure that science based decisions regarding vaccine safety and efficacy are made.

The Vaccine Injury Compensation Program should be maintained and strengthened.

The development of safe and effective vaccines during the past 50 years has been one of the great success stories of American medicine. However, there is concern that future contributions of the vaccine industry may be jeopardized by lack of attention to basic issues. Solutions are not easy to come by and a sustained effort, the collaboration of all stakeholders and political will are required.

Chairman TOM DAVIS. Well, thank you, and thank all of you for your testimony.

Let me just, if I could, recognize we have with us today in the back of the room Cub Scouts Pack 1134, Den 7, from the Chain Bridge District. And we are happy to welcome you here today to today's hearing. This is on the flu vaccines in the United States and the shortage we are having.

Let me just start with one question before I recognize Mr. Mica; and this goes really to Mr. Pien. Could you tell us what happened at Chiron's Liverpool facility that ultimately led to the October 5, 2004 license suspension?

Mr. PIEN. Yes, Mr. Chairman. Chiron, as I testified, acquired this facility in July 2003, and the acquisition actually was conditioned upon a successful satisfactory inspection that took place in June 2003. And after we made the acquisition, of course, we continued the investment program, so about another $50 million got into this current facility. Since then, in addition, we recognized that, as the standards of quality will be rising, that we need to build a new facility; and, therefore, we made the commitment of spending $100 million, as I testified, to build an adjacent facility, of which roughly $30 million have now been spent.

We had a terrific 2003 season, as Commissioner Crawford had indicated; we had a 40 percent increase into the U.S. market from that facility over 2002. We had a 30 percent total output increase, some of which of course, went to parts outside of the United States. We found that the facility was viable. We had tremendous confidence in the ability for that facility to continue to produce products. And, of course, you will recall last year at this time we were sitting here thinking about the regionally severe and earlier flu season. So there is indeed a demand in the United States. So that takes us into 2004.

In July 2004 our quality assurance programs identified two consequential batches which failed our standards, and they turned out to be sterility problems. We then formed a team to identify the root cause. In late August I was advised that we would likely be delaying the shipment of Fluvirin relative to our previous release forecast. We immediately informed both regulatory agencies, MHRA and the FDA, of the expected delay and our adjusted forecast of supply. This, incidentally, led to a press release in August. Since then we have been in regular consultation with both agencies to update them on the progress of our confirmatory testing program, and has brought us now to September 27th.

On September 27th our internal testing program concluded favorably. We expected, therefore, to be able to supply between 46 and 48 million doses to the United States. We initiated a process of reporting the outcome of our confirmative testing program to the regulatory agencies, starting with the MHRA. The MHRA came to visit our Liverpool facility on September 28th to both evaluate our confirmative testing findings and to start what turned out to be a 3-day inspection. When the inspection was completed on September 30th, we received a one-page list of observations and we responded to those observations 4 days later, over the weekend; and that took us to October 4th.

On October 5th the MHRA advised us of their decision to temporarily suspend our Liverpool plant license. And as a consequence of that decision, our products that were produced, that were tested, that were retested could not be and were not released to the marketplace.

Chairman TOM DAVIS. Thank you very much.

Mr. Mica.

Mr. MICA. Thank you, Mr. Chairman.

Dr. Klein, thank you for your very succinct and direct recommendations as to what we need to do to get flu vaccine and vaccine manufacturing in the United States. You covered incentives, which were also mentioned by the producer of the FluMist. You talked about stockpiling a bit. You talked about two things that I got into; I didn't have a lot of time: regulatory reform and liability reform.

The other thing, Mr. Chairman, that I think he brought up, as well, was a meeting of stakeholders. These hearings are nice and they make nice fare; tomorrow it will be a great headline to bash the FDA, but it doesn't get flu vaccine or other vaccines that are essential on the market. But a stakeholders meeting would be very good, where we had people who actually manufacture and produce this, maybe with some of the FDA folks. I think, Mr. Chairman, that would be an excellent recommendation. And, actually, the Virginia health representative said that Congress needs to take steps, and we do need to take steps. We are already into another season.

But you pointed out something, too. I am a fairly ignorant Member of Congress, as has been pointed out here, but you did highlight one area that I am not that familiar with, and that is the difference between regulation of a pharmaceutical and a vaccine. And maybe it is time, as you pointed out in your testimony, that we reexamine the regulatory regime we have. And that may be out of the purview of our committee's jurisdiction, but it is one of the things that we haven't looked at, and you might want to address it. You probably share my ignorance in thinking that liability or the threat of liability, if we could remove that, would also enhance manufacturing, but I guess we are both probably at the school and lacking in knowledge.

But I think you hit the nail on the head, doctor. It is too bad you are the last witness, but I think everything you pointed out succinctly, again, directly identifies the problem and where we need to go. So I thank you for that.

How would you compose a stakeholder conference or meeting? And I think we should do that sooner rather than later, but give us your idea so we could do something positive. And Congress must act, as Dr. Stroube has pointed out.

Dr. KLEIN. Well, I think your remarks are very appropriate in the sense that you would like to see action, and you would like to have knowledgeable people involved; and that would include not only manufacturers, but purchasers, consumers, legislators, or legislative staff that would convene a session that would have contrary proposals as the goal. Then to bring those proposals to this committee or any other body for review and potential action. But I think as a citizen without legislative background, I think we need action, and we want to propose that be moved forward as expedi-

tiously as possible. And I think in a way the flu crisis that we have now is an opportunity to light a fire, because what is coming could be much worse.

Mr. MICA. And Mr. Pien talked about the pending pandemic.

Dr. KLEIN. The pandemic flu problem is inevitable. It is not a question of whether——

Mr. MICA. It is when.

Dr. KLEIN [continuing]. Is it a question of when.

Mr. MICA. Again, you have to excuse my ignorance; I am not very knowledgeable about some of the regulatory process. But, again, the point that you raised about treating vaccines differently from pharmaceuticals—and, again, I am not an attorney like some of these folks up here, I am just sort of a leftover businessman. But the question I would have is, from a technical standpoint, does FDA have the authority to make those changes in that regulatory distinction, or is that something that would require a change in the law?

Dr. KLEIN. I am not sure, but I think FDA——

Mr. MICA. Oh, another ignorant guy. I am sorry.

Dr. KLEIN. But I think they do have the regulatory authority to modify——

Mr. MICA. But I think that is an important question, too, that we should look at and maybe we need to address.

Thank you, Mr. Chairman.

Dr. KLEIN. I think they can modify their inspection.

Chairman TOM DAVIS. Thank you.

Mr. Waxman, you are recognized for 5 minutes.

Mr. WAXMAN. Thank you very much, Mr. Chairman.

Mr. Pien, when FDA inspected the Liverpool facility in June 2003, the agency found 20 serious areas of concern. We now know that the inspectors believed that official enforcement action such as a public warning letter was justified. Had a warning letter been issued, the agency would have detailed the changes necessary to fix the problems identified. But a warning letter was never sent; the inspectors' recommendation was downgraded. As a result, Chiron never received from FDA a specific list of changes needed to fix the problems at the June 2003 inspection.

That raises the question of whether Chiron, which was in the process of taking over the Liverpool facility, really understood what was needed to resolve these concerns. On June 27, 2003, Chiron wrote to FDA asking for a meeting "as soon as possible" to discuss the company's response to the June 2003 inspection. Would this meeting have been an opportunity for the company to learn more about what steps were needed to correct the problems at the facility?

Mr. PIEN. Mr. Waxman, as I testified before, the inspection took place in June 2003, and the Liverpool facility was then not owned by Chiron, it was known by an English company called PowderJect. Our board of directors conditioned the acquisition of the Liverpool facility on what was reported to us to be, by the people in Liverpool, a satisfactory FDA inspection. I think that most of the correspondence that arose from that inspection still had the Evans letterhead on it, which was the name of the previous owner relative to the Liverpool facility.

Since then, my understanding is that there had been discussions between our people in Liverpool and the FDA relating to the observations that they made in 2003, prior to our taking them over. And as I testified before, Chiron made a very, very conscious decision that, indeed, we want to remediate against any past observations of deficiencies, and that was the reason that we followed through with the remediation program that went into that facility of $15 million that was spent in addition to the new facility that I talked about.

Mr. WAXMAN. You also, on the same basis, I assume, asked for the meeting with the FDA, so you could find out what they knew about the plant that you needed to correct.

Mr. PIEN. What I understand, Mr. Waxman, is that those conversations did take place. The regulatory contact were based in Liverpool, and those conversations did eventually take place.

Mr. WAXMAN. FDA told us that they never followed up with you. So you have a different view of what happened, that FDA did followup about the June 2003 inspection?

Mr. PIEN. Mr. Waxman, what I understand, what I am told is that around September or October there was a telephone contact for our people to understand how best to proceed with the observations that were made in the June FDA inspection in 2003.

Mr. WAXMAN. A year later, in June 2004, Chiron wrote FDA again asking for a full copy of the final inspection report. While this report does not contain formal recommendations for action, it does contain a number of specific details, including some recommendations that are not included in initial lists of agency observations. Now, according to the FDA staff, this full inspection report should have been delivered to the company in September 2003. But because of confusion within the agency, it was sent 9 months later. I heard that Dr. Crawford even accepted, in response to a question from Mr. Cummings, that this was a mistake.

Can you explain the difference in the point of vaccine manufacturing cycle between September 2003 and June 2004?

Mr. PIEN. I have not seen that document, so I am not sure. I should probably study that document such that I can provide an intelligent answer.

Mr. WAXMAN. Well, if you get a chance to do that, we would welcome your comments for the record.

Mr. PIEN. We shall.

Mr. WAXMAN. Would having the full inspection report 9 months earlier have helped the company understand the FDA's June 2003 inspection better?

Mr. PIEN. Congressman, as I testified just now, I understand there to have been a contact between our Liverpool-based people who were charged with the fulfillment of the remediation against the 2003 inspections, and my understanding is that contact did take place.

Mr. WAXMAN. The documents we released today show that FDA's regulatory approach from June 2003 to October 2004 was to rely on company representations rather than conduct its own inspections to make sure the problems were being corrected. For example, after you announced a problem with contamination in August 2004, FDA chose to rely on a series of conference calls with you into Oc-

tober. But this approach did not work. From the end of August until the British shut the facility, you were telling FDA and the public that the contaminated vaccine was limited in amount and you had every expectation that the rest of the vaccine was on track for this year.

The problem with the FDA approach is when what you said turned out to be wrong, things were not OK, both British and FDA inspectors found systemic problems, including failures to address high bio burdens, problems addressing connection between tanks and sanitary practices that were found on previous inspections. So FDA was taken by surprise when the British came in and found out these problems.

It seems obvious to me if we had known earlier, we could have planned for the shortage. But, if you know, why did the company provide FDA with information and projections that turned out to be wrong; was it deliberate, or would it be fair to say the company was not aware of the severity of the problems and was optimistic any problems could be overcome?

Mr. PIEN. Congressman Waxman, as I know you know this, the making of the flu vaccine is a terribly complicated thing; it is a new product every year, it is actually one product made up of three components every year. And you start, therefore, with a very large number of eggs, you put these seeds of viruses into the eggs and you make it grow, and then you harvest it. And the process is complex, and that is the reason that you would have, as a manufacture, these series of procedures for testing and retesting.

In July 2004, as I testified before, our quality assurance program identified two batches of products that had sterility issues, and when that occurred, we thought that the scope of the problem did not appear to threaten any supply expectations that we had at the time, and we began to test and do these programs and investigate what caused it, the so-called root cause diagnosis and determination. And as you would expect in making flu vaccines in the way that I have just described—by the way, at the peak of the production season, one can be talking about 400,000, 500,000 eggs. So what you alluded to is the bio burden issue—I think Commissioner Crawford has already testified—happens. The trick is to make sure that you have a robust process that, therefore, the end product does not have any of this bio burden.

Therefore, we expected some failures in these internal testing programs, and that is why we were performing these confirmative tests.

Mr. WAXMAN. You thought they were isolated failures.

Mr. PIEN. We did.

Mr. WAXMAN. But you didn't think they were systemic problems, which, of course, the FDA report seemed to indicate.

Mr. PIEN. We understand that. And as I testified before, this came to us as a surprise. When it came on October 5th, when the MHRA had, as previously agreed, come to take a look at our confirmative testing results, they said they would come; they came. The day after we finished the testing program they came and looked at our results and did a 3-day inspection. At the end of the 3-day inspection we were given one sheet of paper showing us some of the observations, which we responded to within 4 days; and the

day after that the MHRA concluded that there are issues with respect to the systems and processes of the entire plant.

Mr. WAXMAN. Well, my concern—and I see my time is up—is that you were taken by surprise, the Food and Drug Administration was taken by surprise, and yet there had been an evaluation done in 2003 that showed systemic problems. And I don't think that the Food and Drug Administration followed through. They should have been more on the case. You were taking over the company, and they should have been working with you together to make sure that these problems were dealt with. But when you had an increase in production and systemic problems, it just led to what now looks an inevitable, in retrospect, breakdown in the system.

Mr. PIEN. Mr. Waxman, if I may point out the obvious. We are in a regulated industry. So if you are asking me to criticize our regulators, that simply isn't something that I can do, will do, or shall do. Look, we have a plant. We have a set of procedures.

Mr. WAXMAN. Let me interrupt you. I am not asking you to criticize the regulators. I will do that job, because I think they deserve criticism. But I think it would be interesting to know if you had their observations early enough, whether you could have done something about the problem. And I would submit that it just makes sense that if you are not told there is a problem, you may or you may not catch it. But FDA's job should have been to be on the case to make sure these problems were dealt with.

Mr. PIEN. Mr. Waxman, if I may. Here is our situation now. We lost our license for this 90-day period. We are trying to get it back. Now, we are going to do everything we can, that we can define. Once we define those things that we can, we will do those things subject to our assessment that we can actually do them. And I think what is extremely encouraging is that both the MHRA and the FDA have looked at this issue and this situation and this experience, and the two agencies, as I testified before, are working extraordinarily closely. So to the extent that your observations should inspire some lessons for all of us going forward, I think that inspiration has already been achieved.

Mr. WAXMAN. Well, I thank you for that. That certainly is what we want, in the future, to have the problems corrected. I just want to make sure that people understand the mistakes that were made in the past so that they are never repeated again, and that we have a regulator that is doing a good job of regulating, because the purpose of it is to protect the public.

Mr. PIEN. We concur.

Chairman TOM DAVIS. Thank you.

Let me say to my friend, Mr. Waxman, in my opinion, after listening to everything today, there is no question that had the FDA gone in early or the MHRA gone in earlier and alerted them, we might have been able to avert this. But that was not part of their protocols at the time. I think they followed the protocols, as I understand it. It doesn't mean they couldn't have done more, or in the future shouldn't. And I think maybe one of the lessons coming out of this, particularly for foreign vaccine manufacturers, we need to be more vigilant and have more rigid protocols.

Mr. WAXMAN. If you would just yield to me.

Chairman TOM DAVIS. Sure.

Mr. WAXMAN. Their protocols call for what they did, but they also call for an enforcement letter if it is more serious. And I would submit that this is not Rogaine, a product which I didn't use in time. But this is a product that is essential to the health of millions of Americans to avert the flu and the consequences for those who are at risk. And there should have been a higher priority and concern over the flu supply than to treat it in the same routine way they might treat Rogaine and other drugs that don't have the consequences of failure in this case.

Chairman TOM DAVIS. Well, that is certainly a propecious comment. But I think FDA and Chiron have basically said to the committee that the inspection didn't show systematic problems in 2003.

Is that correct?

Mr. PIEN. That is our understanding from the people who experienced the inspection.

Chairman TOM DAVIS. And we may have a difference of interpretation here, but——

Mr. WAXMAN. Well, we will let the documents that we put out today speak for themselves.

Chairman TOM DAVIS. Exactly. And it may be an interpretation——

Mr. WAXMAN. Because the FDA inspectors thought otherwise.

Chairman TOM DAVIS. But I think the testimony is pretty clear that after they went back, as they do, and examined these, the biogenics, and they came back and talked about it, they decided it wasn't. But I think the documents will speak for themselves. We need to move forward. And I think, Mr. Waxman, one thing you have contributed very positively today is the fact that we need to be more vigilant in these areas. And whatever the protocols were, they need to be tweaked at this point, as we move forward. We cannot allow this to happen again. And had we had earlier inspections, not only would Chiron maybe saved a boatload of money, but we might have had more vaccine available to people this year.

Let me just ask a few more questions, if I can. I haven't had my 5 minutes yet.

Mr. Tierney, go ahead. Then I will wrap up. Go ahead.

Mr. TIERNEY. I don't think I am going to take a full 5 minutes, Mr. Chairman, and I thought you had your 5 before.

Let us segue into looking forward a little bit.

Dr. Coelingh, am I saying that correctly?

Ms. COELINGH. It is Coelingh.

Mr. TIERNEY. Coelingh. I am sorry. You talked about what we might do in terms of going forward to make sure that we have enough vaccine on the market. This, so far, has been an industry that has been market-driven, as opposed to government-driven or having government intervene other than the regulatory process. You talked about seeking tax incentives. Well, that obviously would take it outside the free market aspect. You talk about government stimulating demand. That would take it outside the free market aspect on that. So if industry can't survive or can't expand in a free market environment, and if you are going to ask taxpayers then to sort of use their tax dollars to invest in the industry, either by tax incentives or by mandatory public purchases, what do you think

the industry would offer back to those taxpayers or investors as compensation or as a dividend for that? Would they offer up a share of the profits; would they talk about price controls and a guaranteed supply; would they talk about tighter safety regulations; would they talk about contributions, as Dr. Klein talked about, in terms of a VIP type of situation in case there is an error or injury to somebody? Would they talk about all of those or some combination?

Ms. COELINGH. Well, one thing that this industry—I think that is really misunderstood about how the vaccine, especially the flu industry vaccine operates, is that it really is different from a lot of other things where you say a free market system.

Mr. TIERNEY. You operate for a profit, right?

Ms. COELINGH. Correct. But what drives this market is the recommendations of public health authorities. That is the major driving force in deciding who gets vaccinated and who does not.

Mr. TIERNEY. Can I just back up for a second? I think what drives it is individuals that either subscribe to get the vaccine or they don't, and their decision may be driven by some comments or decisions that the government makes, right?

Ms. COELINGH. Correct. It is primarily the Advisory Committee on Immunization Practices. They put out a list of who should and who should not get vaccine every year. And the American Academy of Pediatrics and the American Association of Family Practitioners also follow in step with those recommendations.

Mr. TIERNEY. Is that terribly different than companies that sell things for lowering your cholesterol, where the FDA and other advisory groups put out a word saying that you ought to take these medications to lower your cholesterol?

Ms. COELINGH. The main difference is when you are ill and you need to get a drug to change that situation, it is a lot different than—most of us are walking around perfectly healthy, there is nothing wrong with us except influenza will be coming. So there is an additional——

Mr. TIERNEY. Well, I am just carrying forward my example. Most people walking around with high cholesterol are feeling great and not thinking there is anything imminent there either.

Ms. COELINGH. True. But those medicines are prescribed for a condition; whereas, we are in the area of preventive medicine. So there is a higher hurdle to get people to value influenza prevention and——

Mr. TIERNEY. Now, other industries would advertise.

Ms. COELINGH. Correct.

Mr. TIERNEY. Do you?

Ms. COELINGH. Last year was our launch season, 2003, and during our launch season we did.

Mr. TIERNEY. I don't mean to tag it all on your company; I am talking about the industry. So I want to remove that from anything person on that.

Ms. COELINGH. Yes, there is some advertising. But primarily what happens is the guidance from the CDC and their advisory committees tell doctors who gets vaccine and when they get them.

Mr. TIERNEY. But the industry could advertise, as other industries do, if they want to drive a market, right?

Ms. COELINGH. Correct. Absolutely. But how vaccines are used is not usually driven by direct-to-consumer advertising.

Mr. TIERNEY. I understand there is some difference on that. But if you chose, in a free market environment, to advertise to drive your market, then that would be one way to do it. You are saying that your industry thinks it better to either have taxpayer incentives of some sort or public purchases. So my question that we haven't answered yet, and I would like to get to, is what would the industry offer back?

Ms. COELINGH. What the industry offers back is new and improved vaccines that really will change how medicine is practiced in the United States. We haven't had great changes in our vaccine industry——

Mr. TIERNEY. Couldn't we get that just by having NIH do the research?

Ms. COELINGH. By having, I am sorry?

Mr. TIERNEY. NIH or some other entity do the research.

Ms. COELINGH. Well, you know, NIH does a great job at doing research, but they don't make vaccines.

Mr. TIERNEY. Well, we could either give them the authority to or establish somebody that does, right?

Ms. COELINGH. Well, that comes at a price as well.

Mr. TIERNEY. But I guess what you are telling me is the industry doesn't feel it would owe anything back to the taxpayers if the taxpayers became their investors.

Ms. COELINGH. I am not saying that we necessarily feel that the government has to purchase strategic reserves or purchase unused vaccine. We would much rather make vaccine and have it used than stockpiled and maybe never used.

Mr. TIERNEY. But the two things that you did recommend, one was tax incentives, which would be a taxpayer incentive; the other was public purchases for school children or whatever.

Ms. COELINGH. It is a universal recommendation for children.

Mr. TIERNEY. So, again, why are you putting that burden on the government for an industry that usually are talking all about the free market? Why not advertise and take it upon yourselves to use your investment and your stakeholders' investments to do that?

Ms. COELINGH. Well, first of all, we have invested alot in this product, and, second, if the U.S. Government invests in this product, what they get is they get to not have this kind of situation happening again.

Mr. TIERNEY. But there are a number of ways to skin that cat, right?

Ms. COELINGH. And you get to not have to face the pandemic without having a vaccine as well. So I think those are things that are hard to appreciate because you don't worry about them until they happen, and that is the whole problem with prevention.

Mr. TIERNEY. I guess I don't want to drive too fine a point on this, but let me just drive a real fine point.

Ms. COELINGH. OK.

Mr. TIERNEY. If we make you fabulously wealthy because you have all of these new customers or whatever, or you get tax breaks, why would a taxpayer not expect something back? Apparently you are not going to answer, and that is fine, but that would be the

question I would have, and I would think a lot of taxpayers have. If you are going to go out there and make a profit from the taxpayers' investment one way or the other, then why wouldn't they get some guarantees back that would be of value to them.

But thank you for your colloquy.

Chairman TOM DAVIS. Thank you.

It would probably be cheaper to do it through tax incentives than direct purchase, but that is an economic argument that we could get into.

Let me ask each of you a few questions. Let me start, Dr. Coelingh, with you.

MedImmune right now is looking for universality, is that correct, in terms of being able to market it to everyone and getting those protections?

Ms. COELINGH. Correct. We think that is a good solution to stabilize the market.

Chairman TOM DAVIS. Oh, it would be a wonderful solution. You heard the FDA Acting Director today talk about how they were working toward that. Are we getting satisfaction working toward that? Is there anything we can do to try to move that along?

Ms. COELINGH. Well, the Advisory Committee on Immunization Practices started talking about moving toward a universal recommendation a couple of years ago, and I think there is a lot of support amongst the scientific community and the medical community and the public health community. I think there is a desire to want to do that because we appreciate what could be accomplished by those means. However, I think it comes down to it is going to have to be supported by a lot of education for people to understand, No. 1, why is influenza a problem, because often it is thought of as just a minor cold. We don't realize that 36,000 people die in the United States every year from complications due to influenza and another 200,000 are hospitalized every year. Look at the cost of that to our society. So I think we need to educate people so that they understand how important it is to protect our citizens.

Chairman TOM DAVIS. You also, in your particular product, are trying to make sure that this would immunize older patients and younger patients. There is no evidence that it doesn't, it is just that the burden of proof is on you to show that it does, is that correct?

Ms. COELINGH. We are trying to expand our indication down lower, below the age of 5.

Chairman TOM DAVIS. And higher.

Ms. COELINGH. And higher. So we have recently submitted new analyses of data that we have to show that the product is effective in adults from 50 to 64 years of age, and the FDA should be reviewing that soon.

Chairman TOM DAVIS. Where is your plant?

Ms. COELINGH. Well, our manufacturing is done in three stages. The first stage is manufacturing of the seed viruses, which Mr. Pien has referred to; and we do that in northern California, in the Bay Area. So the seeds are made there. Then those are shipped to Liverpool and our bulk manufacturing is done there. And then the bulks are shipped to our Philadelphia plant and they are blended and filled into the nasal sprayers.

Chairman TOM DAVIS. These are global viruses, then, as they move through. Well, thank you very much. We appreciate everything that you are doing.

Mr. Pien, let me ask, the suspension of your license hasn't prevented you from procuring the materials necessary to move forward next year. You are planning as if you are going to go full boat, correct?

Mr. PIEN. What we are doing is we are defining all of the details of the implementation to achieve remediation, and it is going to take stages, and the first stage is to get the MHRA to come back into our plant, probably in December, to look at whether or not they are going to be able to allow the 3-month suspension of license to expire.

Chairman TOM DAVIS. But you have the eggs lined up and everything as if you are ready to go, right?

Mr. PIEN. Yes.

Chairman TOM DAVIS. And, in fact, if you don't get licensed, you are stuck with a lot of eggs. You will be in the chicken business, won't you?

Mr. PIEN. Well, we will be in a different business than vaccines, yes.

Chairman TOM DAVIS. So we appreciate that is a considerable risk for your coming, just moving ahead in a case like that.

Mr. PIEN. We recognize that.

Chairman TOM DAVIS. And I think we appreciate and I think it shows the can-do attitude here as we move forward, but I just wanted to point that out. You feel encouraged in your work is that fair to say, with MHRA and the FDA, to ensure that you will be able to manufacture for next year?

Mr. PIEN. We feel encouraged in the approach that I have outlined in my testimony has received considerable positive and constructive feedback from both the MHRA and the FDA.

Chairman TOM DAVIS. The issues that were identified that led to the suspension of the license were not facility issues, were they? Weren't there more management issues, human factors issues?

Mr. PIEN. Chairman Davis, that is largely correct. The MHRA did make some recommendations as to whether or not this machine should be here and that machine should be there, and also made some observations about our quality control system and testing program. All of those things are in the scope of our remediation plan proposal.

Chairman TOM DAVIS. And let me just say for the record we met with the FDA and we met with the MHRA, and everybody working together on this felt pretty good about where we are going, but, as you said, there are no guarantees in this business.

Mr. PIEN. No guarantees, first of all, but absolutely. And I think everybody has heard Mr. Waxman's suggestions about learning from our mistakes.

Chairman TOM DAVIS. I have heard a lot of them here too.

Dr. Stroube, how is Virginia doing at this point? Is the CDC making sure we are getting enough to take care of our vulnerable population?

Dr. STROUBE. We are getting our fair share; they are allocating it by population. And with this new data base and today triggering

the ordering thing, ordering part of it, we will be able to do the best we can with the limited vaccine that is available.

Chairman TOM DAVIS. How is the vaccine dosage distribution information on the Flu Vaccine Finder working? It is only available to State health officials. Is that working satisfactory, from your perspective?

Dr. STROUBE. Yes. It is getting better. Like I said, they upgraded it this morning before I left, and I played with it some, where you can go in and actually now we can approve the ordering of vaccine and direct where it goes to on that system through the distribution and through Aventis.

Chairman TOM DAVIS. You notice some other States have gone out and gone to other foreign manufacturers that are not licensed by FDA, but FDA, we heard today, is looking at trying to give them some certification so that they can bring it in. Has Virginia given any thought to doing that?

Dr. STROUBE. We have talked it over, but we have not done that.

Chairman TOM DAVIS. You think you can get an adequate supply for the vulnerable population without doing that?

Dr. STROUBE. Well, we were worried about the timeliness since we were working with what we have to get it out, because we were really worried. We have had some cases in nursing homes already, so we went ahead and used some of the vaccine that we already had gotten for the public health side and just diverted it right away to the nursing homes to try to get them protected. So we have been working with what we had, and with the expectation a foreign vaccine does get approved, it will be put through the CDC system, as I understand it, the same way, and we should get a share of the 5 million that FDA is working on.

Chairman TOM DAVIS. Thank you.

Dr. Klein, current flu vaccine recommendations cover people under the age of 2 and over 50 to include people who have underlying medical conditions and put them at high risk. Do you think the current flu vaccine recommendations are adequate, or should they be expanded to recommend it for all Americans?

Dr. KLEIN. I think the group is at risk, those that have been targeted and those that had the highest hospitalization rates, the most morbidity, and the elderly, the mortality, but I think it is a matter of cost-benefit for employers who have employees who may have to miss work. Certainly we make it a matter of importance that all health personnel be immunized so not only do they stay on the job during an outbreak, but they don't pass on the virus to their patients. And I think the same arguments could be made in almost every venue, that the importance in preventing disease, in this case respiratory disease, does have a cost-benefit and would be beneficial to all ages.

Chairman TOM DAVIS. So an ounce of prevention is worth a pound of cure.

Dr. KLEIN. It will be exam times; college students should be protected.

Chairman TOM DAVIS. Would a universal flu vaccine recommendation also help ensure a stable flu vaccine supply?

Dr. KLEIN. I think so, in the sense that one of the goals, I think, of any program that addresses these issues should be to engage ad-

ditional manufacturers, particularly domestic manufacturers, and if they have guaranteed market with some price structure that makes it profitable, I think they will return to the market and make that vaccine available. And then there will be flexibility, so that if there is a problem with one manufacturer, it will influence modestly the vaccine supply.

Chairman TOM DAVIS. You all have heard everybody's testimony today, the first panel with the FDA and the CDC and everyone else. Are we missing anything here? Is there anything else we ought to be doing that hasn't been discussed or recommended?

Dr. KLEIN. No, but I hope the various authorities, bodies of importance, direct long-term measures, not just to put out this fire, but to consider that this probably will occur in the future; that vaccine shortages have taken place in the past, the current one is important, and they will take place in the future unless we build in some new safeguards against that. But that will take a lot of perseverence and continued interest.

Chairman TOM DAVIS. Thank you.

I would ask unanimous consent that the three statements previously submitted to the committee be entered into the record. Without objection, so ordered.

Mr. Waxman, do you have any followup questions?

Mr. WAXMAN. I do, Mr. Chairman. It is interesting to take note of the fact that we have a crisis right now; we have an inadequate supply for the flu season for the vaccinations. Yesterday a committee of the Senate held a hearing; today this committee is holding a hearing; tomorrow there will be another committee in Congress holding a hearing, it is a subcommittee over in the Energy and Commerce Committee. Obviously, Congress cares a lot about this issue, appropriately so. We want to learn from our mistakes.

But I want to ask you, Dr. Klein. You are one of the leading experts in childhood infections and you served on the National Vaccine Advisory Committee. We are acting as if this has never been an issue, that suddenly we have a whole issue of vaccine supply and we never imagined we would have such an issue before us. Didn't the Advisory Committee present a report in October 2002?

Dr. KLEIN. It did, and many of the issues that I addressed are those that have been partially addressed, such as there was additional funding made available for vaccine stockpile. But because of the SEC regulation, that hasn't been implemented. But the others, because they are complex and they require perseverence, have been managed in a stop gap measure. And we need to reinstitute a more durable set of advisory groups that will be able to address and propose specific recommendations that can alleviate the long-term problems.

Mr. WAXMAN. So before October 2002, your Advisory Committee was looking at the issue of how to give the right incentives for manufacturers to want to invest in producing vaccine, to make sure that they would have a sufficient supply, that the unsold batches wouldn't be a disincentive for them, for example. So the recommendations were made to set up a committee to look at and give further thoughts to it, is that what happened in October 2002?

Dr. KLEIN. Well, actually, the workshop was in February 2002, and as a result of that there was an IOM report of financing vac-

cines that was issued, but it in itself wasn't complete or wasn't sufficiently complete, and was somewhat controversial. So you need continuing activity to maintain until proposals that are satisfactory can be given to this committee and others.

Mr. WAXMAN. So the Vaccine Advisory Committee proposed a multi-disciplinary committee to be operating on an ongoing basis to address these issues of vaccine supply.

Dr. KLEIN. That is correct.

Mr. WAXMAN. Now, what happened to that recommendation, was it adopted?

Dr. KLEIN. The recommendation for the ongoing——

Mr. WAXMAN. Yes.

Dr. KLEIN. The IOM report was issued in the latter part of 2003. In June 2004 there was an NVAC meeting that was specifically held to continue that dialog, and we are interested now in progressing further so that something can be done. But the Vaccine Advisory Committee is just that, it is advisory to the National Immunization Program and the Assistant Secretary of Health and Human Services.

Mr. WAXMAN. Well, we need the advice from the experts, and we had an advisory committee who gave us recommendations; we had the Institute of Medicine give us recommendations. But from what I can tell, none of these recommendations have been followed up on, especially in this area, where everybody is now for giving incentives for production of vaccine so we won't lose supply and face the problem we are facing now. Even Secretary Thompson seems to be talking about the importance of financial incentives.

The point I want to make is we shouldn't wait for a crisis. We have advisory committees. In fact, your testimony here today is helpful, but it is advisory to us in many ways to have Congress act. And if Congress only holds a hearing while there is attention paid to the issue, and if the Secretary of Health and Human Services only pays a high priority to this issue when there is a crisis, and when there is no crisis it is pushed aside, it is inevitable we are going to come back and repeat the same mistakes over and over again.

Let me just ask you parenthetically, because you know this issue very well. Is liability a strong disincentive for the manufacturing of flu vaccine?

Dr. KLEIN. No, it is not.

Mr. WAXMAN. It is not? Why not?

Dr. KLEIN. The flu vaccine, for the most part, has been a very safe product; it is made in eggs, so anybody with an egg allergy would be excluded from getting the vaccine. And there have been minor problems in the past. There was one experience with swine flu, where there was a neurologic disability that followed. And there are a couple of minor issues that occurred. But the reason for this current shortage is not liability, it is associated with a problem that Chiron experienced. That there are ingenious ways of getting around the current legislation and the Vaccine Injury Compensation Program is a given, and that is why that program needs to be reviewed constantly and assured that it remains as strong as it has been in helping the administration of vaccine, those who admin-

ister vaccines, as well as the manufacturers, be clear of liability for approved vaccines.

Mr. WAXMAN. Well, I think you are absolutely right on that, and I hope we will get to—not on this committee, but on the committee that has jurisdiction, although this committee did come up with some recommendations on the Vaccine Compensation Program.

Mr. Chairman, I want to thank you for holding this hearing, and thank all the witnesses for their testimony. I hope we can learn from this experience that we are facing now to do things better and to learn from our mistakes, and hope that we don't make the same mistakes again, and the ones we do won't have the catastrophic consequences that we seem to be facing with so many at-risk people having flu vaccine completely unavailable to them.

Chairman TOM DAVIS. Well, let me thank this panel not just for testifying here today and sharing your views, but what you are doing outside of this hearing room, trying to get more vaccines to people in need. Thank you very much.

The hearing is adjourned.

[Whereupon, at 4:55 p.m., the committee was adjourned.]

[The prepared statements of Hon. Christopher Shays, Hon. Tom Lantos, Hon. Major R. Owens, Hon. Edolphus Towns, Hon. Carolyn Maloney, Hon. Elijah E. Cummings, Hon. Dennis J. Kucinich, Hon. Diane E. Watson, and Hon. Michael C. Burgess, and additional information submitted for the hearing record follow:]

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Statement of Rep. Christopher Shays
November 17, 2004

The most imminent biological threat facing the United States, and the world, today is pandemic influenza. By many accounts, it is overdue. The cyclic emergence of a mutated viral form has caught the world unawares before, and it appears we are once again ill-prepared to meet a likely, perhaps inevitable, public health crisis. This Committee's investigation is leading the way in finding gaps in current vaccine procurement systems and pointing the way to needed reforms.

Two years ago, the world conducted an involuntary, live-fire exercise of public health capacity against the spread of new infectious diseases. Severe Acute Respiratory Syndrome (SARS) emerged from the microbial hothouse of the Far East through the same vulnerabilities and vectors Mother Nature, and skilled terrorists, would exploit to spread genetically altered diseases.

That episode should have alerted us to persistent weaknesses in public health surveillance and vaccine production surge capacity to meet emerging threats. But today we find ourselves still at the mercy of foreign regulators and volatile international markets in trying to meet the threat of infectious diseases.

In a world made smaller by the speed of international travel and the rapid mutation of organisms in our crowded midst, the interval between local outbreak and global pandemic is shrinking. Virulent, drug-resistant organisms easily traverse the geographic and political boundaries that still define, and inhibit, public health systems.

In this perilous environment, the lack of vaccine supplies has never been more dangerous. The need for vaccine research and rapid-response production capacity has never been more pronounced. And the vigilance of biomedical regulatory processes has never been more critical to public health and national security.

Opening Statement of
Rep. Tom Lantos
Government Reform Committee Hearing on
"The Nation's Flu Shot Shortage: Where Are We Today
and How Prepared Are We For Tomorrow?"
November 17, 2004, 1:00 p.m., 2154 Rayburn

Thank you, Mr. Chairman and Ranking Member for your efforts today to conduct this important hearing. The flu vaccine crisis gives all of us chills because it represents the failure of federal and state emergency procedures in the face of diseases that can circle the globe. In this day of robust international travel and under the shadow of international terrorism, this has wide-ranging implications.

As a representative from the San Francisco Bay Area, I am deeply disturbed that Chiron, which is based in the community of Emeryville, was not subject to closer federal scrutiny. There was failure to monitor the Chiron's Liverpool plant's progress in putting safeguards in place that were recommended after inspections in 2003. Will Chiron now be able to bring its British facility up to code in time for the next flu season? And if not, can the FDA license another facility quickly enough to ensure there will be enough vaccine next year?

But I would also like to know, as a lot of Americans would, exactly how we got into the situation in the first place where the federal government apparently could not foresee a shortage of such a vital vaccine supply, despite apparent warning signs.

The documents recently delivered to this committee raise serious questions about federal oversight. They show that the authorities were aware of major problems at the vaccine manufacturing facility as early as June 2003, but missed opportunities to address the problems. I am stunned by this utter lack of action to protect public health.

We need real and effective safeguards so that the source of the vaccine is not limited to such a small selection of manufacturers in the future. Perhaps we should be looking at ways to establish incentives to bring manufacturers into the marketplace, such as tax credits or buy back options that are fiscally and technically feasible. I would also like to examine the possibility of providing the Center for Disease Control (CDC) with additional authority to assist federal and state officials in providing the flu vaccine in a time of crisis.

Opening Statement for Congressman Major R. Owens

Government Reform Committee Hearing
Hearing on "The Nation's Flu Shot Shortage: Where Are We Today and How Prepared Are We for Tomorrow?"
Wednesday, November 17, 2004

Mr. Chairman, this afternoon's hearing focuses on an issue of vital importance to my constituents and the nation at large. The critical shortage of flu vaccine has placed millions of Americans in immediate harm's way. Clearly, we need to get to the bottom of the underlying causes of the current vaccine crisis and take immediate steps to remedy it. To combat a potential flu epidemic effectively; however, we must also tackle without delay the pressing issue of paid sick leave. In America today, **every other full-time worker lacks a single paid sick day**. If such a worker comes down with flu symptoms; she or he will have to choose between losing a day's pay or going to work and risk spreading the flu virus. And some of these workers would actually jeopardize their jobs if they elected to stay home with a bad case of the flu.

With such staggering numbers of workers affected – virtually half the fulltime workforce – the possibilities for spreading a full-fledged flu

epidemic become legion. What will happen if public health officials see serious warning signs of the flu's spread next month and start urging anyone infected to stay home? How can so many workers risk the loss of paychecks or – for some – their very jobs?

By failing to ensure all workers have a right to a minimum number of paid sick days, we run the risk of turning this flu season (as well as other infectious disease risks) – into a crisis with life-threatening consequences. This is an instance where safeguarding the health of the American workforce is directly tied to safeguarding the health of all Americans. Therefore, I ask my colleagues to join me in supporting the Healthy Families Act (H.R. 4575), a bill to provide all workers with the right to paid sick days.

Mr. Chairman, I also ask that several pertinent reports on paid sick leave be included in the hearing record. They are (1) "Sick Days Dwindle, Disappear for Many" – an article that appeared in USA Today on November 12th, (2) *No Time to Be Sick: Why Everyone Suffers When Workers Don't have Paid Sick Leave* – a report issued by the Institute for Women's Policy Research, and (3) *Get Well Soon: Americans Can't Afford*

to be Sick – a state – by – state and federal assessment of paid sick leave issued by the National Partnership for Women & Families.

THE NATION'S NEWSPAPER
USA TODAY
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www.usatoday.com
USA TODAY
Money
SECTION B
Friday, November 12, 2004

Sick days dwindle, disappear for many

Half of full-time workforce receive no paid sick days

By Stephanie Armour
USA TODAY

The flu vaccine shortage couldn't come at a worse time for employees, with cost-cutting employers reducing the number of paid sick days given to workers and curbing other benefits such as emergency back-up child care.

Workplace In addition, about half the full-time American workforce gets no paid sick days, according to the Department of Labor. Part-time employees and those in lower-wage service and blue-collar jobs are the least likely to have paid sick days. The peak flu season is late December and January.

"They're in low-wage jobs and living paycheck to paycheck," says Debra Ness, president of the National Partnership for Women & Families. "They have to go to work sick or lose a day's pay or, in some cases, lose their jobs."

Recent trends:

▸ **Employees have fewer sick days.** Paid sick days have been one of several benefits curtailed by employers in recent years. The number of employers providing paid sick leave dropped from 82% in 2002 to 76% last year, according to the Society for Human Resource Management (SHRM).

Sherry Allen, 35, of Indianapolis was a waitress in a restaurant and had no access to paid sick leave. She worked with strep throat and bronchitis. She says she was fired for taking too much time off to care for her son; she is currently unemployed.

"It's hard to have that fear of losing your job," says Allen, a mother of four boys, ages 18, 16, 12 and 9.

▸ **Employees are less able to save up unused sick days.** Cost-cutting employers are increasingly moving away from benefit programs that allow employees to accrue sick days. Instead, they are turning to a use-it-or-lose-it approach.

▸ **Fewer employees have access to back-up care.** The number of employers offering emergency back-up child care or child care when employees have sick family members has dropped from 14% in 2001 to 9% this year, according to SHRM.

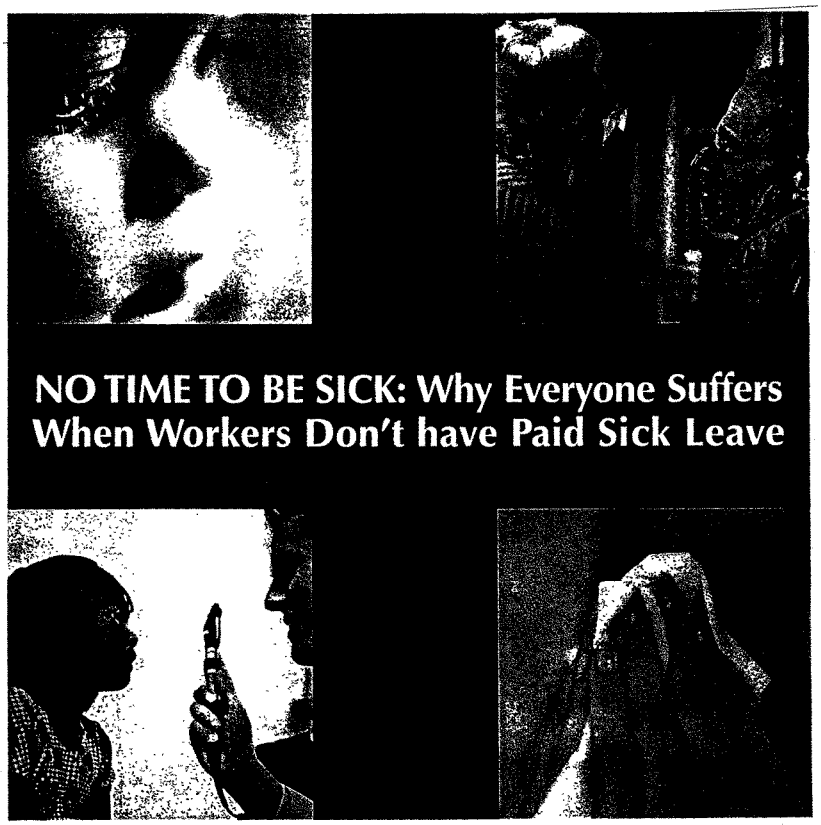
Some employees say they feel pressured not to take time off.

Tanya Frazier says she was fired from her job as an executive assistant after taking time off to care for her 9-year-old daughter, who had the flu. She says she had used all the nine sick days allowed by her employer.

"My boss said, 'You're too dedicated a mother and not dedicated to your job,'" says Frazier, 39, a single mother in Topanga, Calif., who now is a temp.

Some human resource agencies are urging companies to revise their policies to give workers more sick days.

"If the flu really spreads, there will be a strong effort to get people not to come to work," says Lori Rosen, at human resources information provider CCH. "But people want to maintain their jobs, so they work even when they feel lousy."



NO TIME TO BE SICK: Why Everyone Suffers When Workers Don't have Paid Sick Leave

Institute for Women's Policy Research

About this Report

This report was made possible by funding from the Ford Foundation and the Annie E. Casey Foundation. The report was published as a part of IWPR's ongoing project on job quality issues.

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NO TIME TO BE SICK: Why Everyone Suffers When Workers Don't have Paid Sick Leave

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Abstract

Paid sick leave gives workers an opportunity to regain their health, return to full productivity at work, and avoid spreading disease to their co-workers, all of which reduces employers' overall absence expense. When used to care for sick children, it helps them get well faster and reduces job turnover of working parents. Workers who care for adult relatives, including the elderly, need paid sick leave to take care of their loved ones' chronic and acute medical problems. However, new analysis of data collected by the U.S. Bureau of Labor Statistics reveals the inadequacy of paid sick leave coverage: more than 59 million workers have no such leave. Even more—nearly 86 million—do not have paid sick leave to care for sick children. Full-time workers, those in the public sector, and union members have the best sick leave coverage, while part-timers and low-wage workers have very low coverage rates. Expansion of paid sick leave and integration of family caregiving activities into authorized uses of paid sick leave are crucial work and health supports for workers, their families, employers, and our communities at large.

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NO TIME TO BE SICK: Why Everyone Suffers When Workers Don't have Paid Sick Leave

Introduction

Millions of American workers know they can stay home with full pay when they get the flu or need some time off to recover from an injury. Paid sick leave is one of many non-wage benefits whose development was spurred by wage controls imposed during World War II (Schumann 2001, Stelluto and Klein 1990), and many workers take it for granted that their employers will cover their short-term illnesses. Many firms even allow employees to use paid sick leave when they need to stay home to care for sick children or to visit the doctor.

There's another side to this issue, though. In fact, workers' participation in paid sick leave programs is surprisingly—even shockingly—low. No federal law requires that workers receive any paid time off. The latest published data from the U.S. Bureau of Labor Statistics reveal that nearly half of all private-sector U.S. workers (47 percent) are not provided *any* paid sick time (U.S. Bureau of Labor Statistics 2001). And as Figure 1 indicates, employers are actually *reducing* their paid sick leave programs. More and more workers have no paid sick leave and, when they become ill, must choose between going to work anyway or taking unauthorized time off, which may lead to their being fired.

Inadequate paid sick leave coverage causes a number of problems: negative health effects for workers, contagion among co-workers, reduced productivity, higher turnover, lost income, worse health outcomes for children, and increased need for health care resources. Many of these outcomes impose economic costs on individuals, employers, families, and the government. To help understand the connection between paid sick leave and these costs, this report compiles evidence of how these effects are created. It also presents new analysis of national data that investigates the job characteristics that are associated with having paid sick leave, including differences among workers at different wage levels. This analysis includes an exploration of the extent of workers' participation in sick leave plans that can be used to take time off work to care for sick children, a benefit that is increasingly important to parents and children as parents' labor force activity rises.

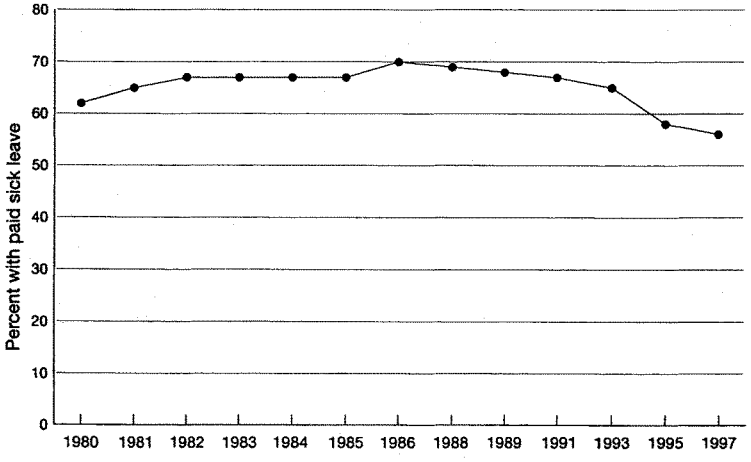
Policy Context

In a market-based economy like ours where most safety net programs are integrated with employment, a good job must provide more than just a decent wage. Affordable health insurance and a secure pension are also typically considered to be components of good jobs. But workers need more than these basics in order to stay healthy and productive. Paid time off work to regain good health following an illness or injury is also essential.

As family caregivers' employment has increased, sick leave can also help workers maintain their work status while fulfilling their responsibilities for caring for sick relatives—especially young children and the frail elderly. The labor force participation of mothers of infants has nearly doubled in the last 25 years, from 31 percent in 1976 to 55 percent in 2002, and nearly 1.3 million women who were employed full-time in 2002 gave birth that year (Downs 2003). Two-thirds (64 percent) of women with children under 6 are in the labor force (Jacobs 2004). Only 30 percent of children between the ages of 6 and 17 have a full-time at-home parent (U.S. Department of and Human Services 2003). Most children cannot safely be at home alone when they're sick, and even for those who can be, being comforted by a parent is important to both parent and child. In addition to the question of children's physical safety (Peterson 1989), it is illegal for young children to be left home alone in many jurisdictions (Kerrebrock and Lewit 1999).

The care needs of the elderly require increasing attention and resources as well, as our population ages. The number of Americans who are 75 or older is expected to more than double between 1990 and 2030; by that time, we will have nearly 50 million individuals aged 65 or older (Employment Policy Foundation 2003). Sixteen percent of Americans 18 and older care for a relative who is 50 years old or older. Families also provide substantial amounts of care for other non-elderly adult relatives. Five percent of adult Americans are caregivers for relatives between the ages of 18 and 49. The average weekly hours of family caregiving for adult relatives amount to a part-time job: 23 hours per week for

Figure 1. Trend in paid sick leave coverage, employees in medium and large private establishments, 1980 to 1997



Note: Data not available for 1987, 1990, 1992, 1994, 1996, 1998, or subsequent years.
Source: Extracted from BLS website, http://data.bls.gov/servlet, July 2, 2003.

women, and 19 for men (National Alliance for Caregiving and AARP 2004).

For many elderly and other adult care recipients, the relatives who provide care are employed. Nearly half work full-time, and another eleven percent are employed part-time. Over 21 million full-time workers are caregivers for elderly relatives. Workers caring for their adult loved ones while also holding down a paid job need work-hours flexibility, including paid time off, in order to perform both sets of responsibilities: Nearly three in five report that their caregiving work causes them to be late for work occasionally, to leave early, or to take time off (National Alliance for Caregiving and AARP 2004). Paid sick leave policies can offer these caregivers an opportunity to help maintain their families' health, by taking them to medical visits and caring for them when they're ill.

Since women continue to be our society's main caregivers—not only for children but also for the elderly, the disabled, and special-needs children (Heymann 2000)—paid sick leave is of particular concern to them. Women with young children have slightly higher absenteeism than those with no or older children, with each child under the age of six adding about 5 percent to the probability that a mother will be absent during a year (Vistnes 1997).[1] Yet women are more likely than men to have neither sick nor vacation leave, and less likely to be able to miss work to care for sick kids (Heymann 2000).

Policymakers in some states (California, Hawaii, New Jersey, New York, and Rhode Island) have acknowledged workers' need for paid time off to attend to their own serious health concerns by enacting Temporary Disability Insurance (TDI) programs. TDI provides partial wage replacement for employees unable to work due to non-work-related illness and injury, including pregnancy- and maternity-related medical disability (Lovell 2004). In 1993, Congress recognized the importance of time off for

workers to care for both their own and their families' critical health needs by mandating up to 12 weeks annually of job-protected leave in the Family and Medical Leave Act (FMLA).[2] As of 2004, California's TDI program, which is paid for by employee premiums, has been expanded to allow up to six weeks of leave per year for family medical care.

Neither TDI nor the FMLA is designed for absence related to the short-term illnesses so common in childhood, for workers' own colds and flus, or for the routine medical visits such as physical exams and well-child appointments that are essential to preserving good health. There are significant precedents, however, for legislation requiring that paid sick leave be available for sick family care. In 48 states (all but Virginia and Louisiana), laws, regulations, or collective bargaining agreements allow state workers to use sick leave to stay home with sick family members (National Partnership for Women and Families 2004). At least five states (California, Connecticut, Hawaii, Minnesota, and Washington) require private-sector employers to allow workers to use paid sick leave (when such leave is provided) to care for sick family members (ibid.). A law passed in Washington state in 2002 authorizes workers with any form of paid time off to use that leave to care for a sick child, spouse, parent, parent-in-law, or grandparent (Watkins 2004). Other states, including Massachusetts, Nevada, and Vermont, have endorsed working caregivers' responsibility for their families' health needs by mandating job-protected leave for family members' routine or emergency medical needs in specified circumstances (National Partnership for Women and Families 2004).

Incidence of Illness Among Workers and Children

Employed adults miss an average of 4.6 days of work per year due to illness or other health-related factors (Lucas, Schiller, and Benson 2004)—just under one week. Women have slightly higher health-related absenteeism than men (5.2 and 4.1 days, respectively, excluding maternity leave). Workers in lower-income families miss more days than those in higher-income families; this is consistent with well-established disparities in health that are correlated with income (see, e.g., Arno and Figueroa 2000). Absence rates are highest for workers aged 45 to 64 years, at 5.7 days per year; lower for younger workers (aged 18 to 44 years), at 4.2 days; and lowest for workers aged 65 and older, at 3.0 days (Lucas, Schiller, and Benson 2004). On average, then, workers need about one week of sick leave per year for their own health needs. Many workers with higher-than-average sickness experience or with severe or chronic health conditions need substantially more than this.

Children aged 5 to 17 years miss an average of more than three days of school per year for health reasons (author's calculation from Bloom, Cohen, Vickerie, and Wondimu 2003). With the school-year lasting roughly three-fourths of the year, this suggests that, on average, parents in families with no at-home caregivers will need to take about four days off annually to care for each school-age child. In a 1990 survey, 18 percent of employed mothers reported having stayed home with a sick child in the previous month (Glass and Estes 1997). Some children have substantially higher absence rates due to health problems—six percent miss more than two full weeks of school (Bloom, Cohen, Vickerie, and Wondimu 2003)—but mothers of children with chronic health conditions such as asthma are *less* likely to have sick leave than other mothers (Heymann, Earle and Egleston 1996). Children of single mothers are more likely to have health-related absences lasting eleven or more days than children living with a married mother,[3] as are children in poor families (Bloom, Cohen, Vickerie, and Wondimu 2003).

Younger children have higher rates of illness than those who are school-age. Infants make more than four times as many ambulatory care visits each year as school-age children, and pre-schoolers see a medical practitioner nearly twice as often as school-age children (Freid, Makuc, and Rooks 1998). Since early childhood education centers typically require children to be symptom-free for 24 hours before returning after an illness (Fleming 2003), one day with a runny nose for a youngster may well cost a parent two days of lost work time. Just taking infants in for well-baby check-ups can be time-consuming; the American Academy of Pediatrics recommends seven such visits in the first 12 months after birth, and three in the following year (Medical University of South Carolina 2001).

The Costs of Not Having Paid Sick Leave

Maintaining workers' health and productivity takes time—a few occasional hours to get routine medical care, and a day or more now and then to get

over a cold or an injury. To evaluate the adequacy of existing paid sick leave policies, it is important to investigate what happens when workers are not provided with paid time off for these circumstances.

Some of the consequences for individual workers are obvious: they either go to work and feel lousy or risk job loss by staying home without authorization from their employer. The effects are felt by many other parties, however, as discussed in this section: employers, colleagues, other family members, children's playmates, and health care practitioners. Going to work when sick exposes co-workers to the risk of becoming ill themselves, while providing the employer with less-than-optimal work effort. Workers who must stay home but have no leave may be fired or suspended. The domino effect of losing a job may lead to loss of health insurance and certainly decreases families' economic stability. Parents and other caregivers who can't stay home when needed may see worse health outcomes for their loved ones, while sick children spread illness to other children in child-care settings. These effects in turn place greater demands on health care resources. And employers who don't provide adequate paid sick leave deny themselves the increased productivity and job retention of more satisfied, healthier, and appreciative workers.

Presenteeism. When workers don't have paid sick leave, their employers and co-workers pay a price. The practice of going to work while ill is known by human resources professionals as presenteeism, and it is not only a poor solution for those who are sick; it causes problems for the rest of their colleagues as well. Workers may feel they can't stay home when they're sick, because of important work that must be completed, to avoid burdening co-workers with extra work, or out of fear they will be penalized for being absent. Not taking time off to regain one's health can actually lead to longer absences, though, as health worsens and minor problems are exacerbated (Grinyer and Singleton 2000.) And despite their show of loyalty, workers who show up while sick are not likely to be able to perform at their usual level of productivity (CCH Incorporated 2003). Total absence time for the employee pool also increases as an illness spreads within the workplace, with additional workers being affected and having to take time off (Skatun 2003).

Employers recognize the effects of this phenomenon: Nearly half (44 percent) report that presenteeism is a problem in their workplace (CCH Incorporated 2003). The value of lost productivity of workers who are on the job when not fully healthy is greater than the combined cost of employee absence and health and disability benefits (Goetzel, Long, Ozminkowski, Hawkins, Wang, and Lynch 2004). Unfortunately, employers' absence reduction programs can have the effect of causing more workers to stay at work when they should be home recuperating (Grinyer and Singleton 2000).

One of the main reasons workers cite for going to work while ill is their need to save their sick leave so they can stay home when their children are home sick (ComPsych Corporation 2004). Eighteen percent practice presenteeism for this reason. Another third (33 percent) feel they have too much work to do to stay home, and a quarter (26 percent) fear taking time off will have negative ramifications for their performance evaluation.

Research documents that paid sick leave policies reduce the rate of contagious infections in the workplace by isolating sick workers at home (Li, Birkhead, Strogatz, and Coles 1996). For sick child leave, the true wage cost of parental absence must be weighed against the impact on a worker's productivity of knowing a sick child is not receiving adequate care when the parent must choose time at work over being at home when needed there.

Job loss. When workers do not have authorization to stay home when they're sick, or when a child is sick, some will have to miss work anyway and end up being fired (Browne and Kennelly 1999, Dodson, Manuel, and Bravo 2002). Family illness is more likely to lead to job loss for women than for men, since the responsibility for caring for sick relatives is still typically placed on women. One case study found that being female doubles the odds of experiencing job termination related to family illness (Spilerman and Schrank 1991).

It is not unusual for employers to restrict their paid sick leave policies to workers who have completed an initial probationary period of employment. For some workers, this creates an insurmountable barrier to successful completion of probation, as children's chronic health needs necessitate taking time off when none is authorized.

When a job ends, so does employer-provided health insurance, leaving workers and their families even more vulnerable to problems in accessing needed health care.[4]

Lost income. Workers who are allowed only unpaid absences when they or members of their families are sick lose the wages they would have received if they could have worked or used a paid time off program. Unapproved absences may also be punished with temporary unpaid suspensions (Dodson, Manuel, and Bravo 2002). Because of the correlation between earnings level and participation in paid sick leave programs (see section on paid sick leave coverage, below), this income deficit is especially likely to be borne by low-income families. Mothers in low-income families are nearly twice as likely as higher-income mothers not to be paid when they stay home with sick children (64 percent and 37 percent, respectively); three of every four poor mothers who miss work to care for sick children receive no wages while off work (Wyn, Ojeda, Ranji, and Salganicoff 2003).[5]

Those fired for taking unapproved time off lose earnings during their entire period of job search. In most states, they will not be eligible for Unemployment Insurance, because the reason for their job termination won't meet qualifying tests (Smith, McHugh, Stettner, and Segal 2003). With unemployment spells now averaging 20 weeks, or nearly half a year (U.S. Bureau of Labor Statistics 2004b), losing a job because of illness can be financially devastating.

Worse health outcomes for children. Having paid leave is the primary factor in parents' decisions about staying home when their children are sick (Heymann 2000). Child care centers typically forbid attendance by sick children, but the reality is that center personnel, who are only too intimately aware of the difficulty their clients face in balancing work and parenting, sometimes bend the rules to help a parent keep their job. Parents desperate to keep a job sometimes leave sick children in child care without notifying the providers of their children's health conditions. (Centers specializing in taking care of sick children are much too rare to help many parents and children.) When parents cannot take time off work to care for sick children, it takes a toll on the health of both their children and their children's playmates. These sick children miss out on the health benefits of being cared for by their parents, leading to worse short- and long-term health outcomes (Palmer 1993). And having sick children in child care has the same effect as having sick adults at work: contagion and overall higher rates of infection for all the children in care (Heymann, Earle, and Egleston 1996).

Without paid leave, parents may postpone or even skip recommended well-child visits. This may interrupt vaccination series, with follow-up shots not received on time, leaving children vulnerable to preventable serious illness.

Greater use of health care resources. Adults and children who have the time and care they need to recover from health problems may use fewer health care resources in the long run. Active parental involvement in children's hospital care, for instance, can head off future health care needs because of increased parental education and awareness (Palmer 1993). In addition, when hospitals include parents in children's care, hospital stays are reduced (Kristensson-Hallstrom, Elander, and Malmfors 1997). Conversely, the failure to provide adequate recuperative time and requisite parental care may tend to exacerbate future health needs.

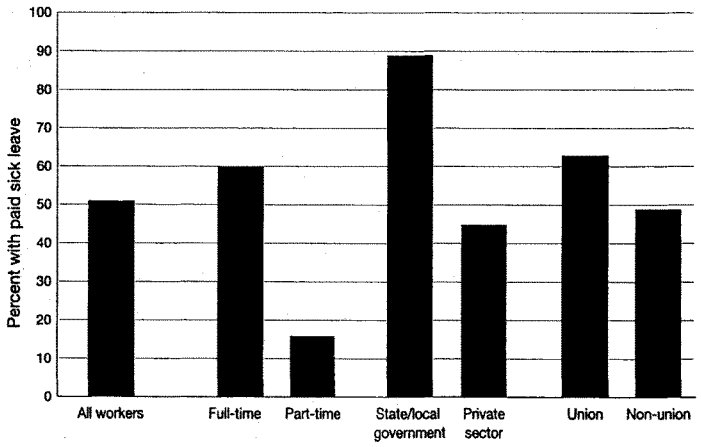
Loss of productivity-enhancing worker loyalty effects. Many theorists postulate that employer practices that help workers combine their care work with employment increase worker productivity (see, e.g., Johnson and Provan 1995). Workers with more flexibility may be less distracted while at work, less exhausted by their combined family and employment work effort, more committed to a valued employer, or more determined to do what it takes to keep a job that fits their lifestyle. Any of these motivations can both enhance productivity and increase job retention, saving employers the cost of hiring and training someone new.

Why Workers Need Sick Leave Even if They Have Vacation Leave

Sick leave serves a different purpose than vacation or holiday time: Rather than rewarding work effort with leisure time, sick leave offers an incapacitated worker an opportunity to recuperate and then return to employment at full productivity. (Vacation and holiday leave also have important recuperative effects, of a kind workers getting over a cold won't experience during their sick leave.) For parents and other caregivers, paid sick leave also promotes the health and well-being of family members.

Employers' rules governing the use of vacation time sometimes make it incompatible with the purposes of sick leave and sick family care. In some firms, workers' requests for vacation leave must be submitted at the beginning of the year and must be

Figure 2. Percent of workers with paid sick leave, by work hours, sector, and union status, 1996-1998



Notes: Work hours are as defined by the individual reporting establishment. "Union" includes all workers whose working conditions are collectively bargained. Dataset excludes federal, military, agricultural, household, and self-employed workers.
Source: Institute for Women's Policy Research analysis of the 1996-1998 Employee Benefits Surveys.

in one-week increments. These rigid scheduling rules cannot respond to the unpredictable timing of health problems.

Who Has Paid Sick Leave?

There is clearly a need for paid sick leave and paid sick family leave, given the evidence presented above that not having these leaves creates problems not only for workers but also for employers, family members, and communities. To explore the adequacy of existing policies and inform the development of more comprehensive programs, the Institute for Women's Policy Research analyzed data on workers' coverage by paid sick leave programs from U.S. Department of Labor establishment surveys conducted in 1996, 1997, and 1998.[6] (The dataset is described in detail in the Appendix.) Taken together, these three surveys provide a nationally representative snapshot of employer-provided benefits available to non-agricultural civilian employees outside the federal government and private household employment.[7] (Information on worker characteristics is not provided by these surveys.) The combined dataset includes 54,247 worker observations for incumbents with positive work hours during the survey period.

This analysis confirms that barely half (51 percent) of all American workers have paid sick leave (Figure 2 and Table 1). More than 59 million workers are not covered by such a policy. Coverage is far superior for full-time as compared to part-time workers: While three in five full-time workers have paid sick leave (60 percent), only one in six part-timers does (16 percent). The rate of paid sick leave coverage in public-sector employment is twice that of the private sector: Nine of ten workers in state and local governments have paid sick leave (89 percent), but fewer than half of those working in the

private sector do (45 percent).[8] Workers covered by collective bargaining agreements are much more likely to participate in paid sick leave programs than those without union representation (63 percent and 49 percent, respectively).[9]

The most common form of sick leave policy offers a specified maximum number of days of time off annually (46 percent of all employees have this kind). For a small minority of workers, sick leave is provided on some other basis, such as policies with unlimited leave available on an as-needed basis.

Differences Among Industries. The adequacy of paid sick leave coverage varies enormously among industries. As shown in Table 2, some industries provide paid sick leave to nearly all their workers: utilities and educational services (88 percent each) and state and local government (87 percent). Several others cover a smaller portion of their workers, but more than half: financial activities (73 percent), information (69 percent), natural resources (63 percent), health care and social assistance (61 percent), wholesale trade (57 percent), and both transportation and warehousing and professional and business services (52 percent).

Following these industries, which provide paid sick leave at or above the average rate of 51 percent, come a substantial number with very poor leave coverage. Retail trade (43 percent), art, entertainment and recreation (40 percent), durable (38 percent) and non-durable (36 percent) manufacturing, and "other" service (31 percent) all cover about a third of workers. In the construction and accommodation and food service industries, paid sick leave is barely present (covering 27 and 14 percent of workers, respectively).

Differences Among Occupations. The adequacy of paid sick leave policy coverage varies considerably among occupations, although not quite as exten-

Table 1. Percent and number of workers participating in paid sick leave plans, by plan type and work hours, 1996-1998

		By work hours: (a)	
	All workers	Full-time workers	Part-time workers
Percent with and without leave:			
Percent with some paid sick leave	51	60	16
By type of plan:			
Specified maximum number of days	46	55	15
As needed, unlimited	3	3	*
Other basis	*	2	*
Percent with no paid sick leave	48	39	84
Number with and without leave (in millions): (b)			
Number of workers with paid sick leave	62.5	58.4	4.1
Number with no paid sick leave	59.1	38.3	20.8
Sample size	46,216	38,548	7,668
Population (millions) (b)	122.0	97.1	24.9

*Less than 2 percent.

(a) Work hours status is as defined by the individual reporting establishment.

(b) Based on size of 2003 workforce. Dataset excludes federal, military, agricultural, household, and self-employed workers.

Notes: Percentages "by type of plan" may not sum to "percent with some leave," nor percent with and percent without leave to 100, due to rounding. Dataset excludes federal, military, agricultural, household, and self-employed workers.

Source: Institute for Women's Policy Research analysis of the 1996-1998 Employee Benefits Surveys.

Table 2. Percent of workers with paid sick leave, by industry and occupation, 1996-1998

Industry	Percent of workers with paid sick leave	Occupation	Percent of workers with paid sick leave
Utilities	88	Executive, administrative, and managerial	73
Educational services	88	Professional, technical	71
Government (state and local)	87	Administrative support, clerks	68
Financial activities	73	Transportation, material moving	47
Information	69	Sales	42
Natural resources (a)	63	Precision production, craft, repair	39
Health care and social assistance	61	Service	37
Wholesale trade	57	Handler, equipment cleaner, helper, laborer	35
Transportation and warehousing	52	Machine operator, assembler, inspector	29
Professional and business services	52		
Retail trade	43		
Art, entertainment and recreation	40		
Manufacturing, durable	38		
Manufacturing, non-durable	36		
Other service	31		
Construction	27		
Accommodation and food service	14		

(a) Includes forestry, fishing, and mining. Data not available for these industries individually due to sample sizes.
Note: Dataset excludes federal, military, agricultural, household, and self-employed workers.
Source: Institute for Women's Policy Research analysis of the 1996-1998 Employee Benefits Surveys.

sively as the differences by industry. The three occupations with the highest paid sick leave coverage rates are all white-collar: executive, administrative and managerial (73 percent), professional and technical (71 percent), and administrative support and clerical (68 percent). In blue-collar, sales, and service-sector jobs, roughly one-third to two-fifths of workers have paid sick leave (47 percent in transportation and material moving; 42 percent in sales; 39 percent in precision production, craft and repair; 37 percent in service; 35 percent in handler, equipment cleaner, helper and laborer occupations; and 29 percent in machine operator, assembler and inspector positions).

Permitted Uses of Paid Sick Leave

By definition, workers may use paid sick leave when their own health problems make them unable to work. Many workers are also allowed to respond to other critical needs by taking time off work under a paid sick leave policy. Table 3 and Figure 3 show the percent of workers, by job characteristics, permitted to use their paid sick leave policy to visit the doctor, to care for their sick children, to handle personal business, or for other purposes. Workers who do not have paid sick leave, or whose policy is limited to workers' own health-related absences, are represented in the last column of Table 3.

Paid Time Off for Seeing a Doctor. One in three workers (33 percent) has paid sick leave that may be used for doctors' appointments. This leaves almost 82 million workers with insufficient paid time off to take care of routine and acute medical care. Full-time workers' ability to use paid sick leave for this purpose is nearly four times as high as for part-time workers (39 and 10 percent, respectively). Access to paid sick leave for doctors' visits is three times higher in the public sector than for private employees (75 and 26 percent, respectively). Being represented by a union increases coverage by about one-third (with coverage rates of 42 percent for union and 31 percent for non-union workers).

Among industries, state and local government (80 percent), educational services (71 percent), and utilities (65) stand out as offering the most substantial leave for doctors' appointments. Roughly 40 to 50 percent of workers in financial activities (51 percent), natural resources (43 percent), information (42 percent), health care and social assistance (38 percent),

Table 3. Percent and number of workers with paid sick leave plans allowing selected uses, by job characteristics and sector, 1996-1998

Job characteristic	Percent of workers in plans allowing use for: Doctors' appointments	Care of sick children	Personal business	Other	Percent not in plans or in plans not allowing any other uses
All workers					
Percent with stated use	33	30	9	5	
Number (millions)	40.3	36.6	11.0	6.1	
Percent without stated use	67	70	91	95	63
Number (millions)	81.7	85.4	111.0	115.9	76.9
Work hours (a)					
Full-time	39	35	11	6	56
Part-time	10	9	4	*	89
Sector					
Private	26	23	8	5	70
State and local government	75	69	18	3	18
Union representation (b)					
Union	42	37	11	3	52
Non-union	31	28	9	5	65
Industry					
Natural resources (c)	43	40	*	7	54
Construction	15	14	3	4	84
Manufacturing, durable	21	18	9	5	76
Manufacturing, non-durable	14	9	4	2	84
Wholesale trade	29	28	10	5	67
Retail trade	21	22	7	6	73
Transportation and warehousing	28	19	9	2	67
Utilities	65	45	6	*	31
Information	42	32	11	6	56
Financial activities	51	47	13	11	41
Professional and business services	36	31	12	6	63
Educational services	71	68	25	4	22
Health care and social assistance	38	36	9	6	54
Art, entertainment and recreation	25	20	11	3	73
Accommodation and food service	5	4	*	*	94
Other service	17	14	6	3	80
Government (state and local)	80	69	7	*	17
Occupation					
Professional, technical	50	47	13	6	44
Executive, admin., managerial	49	44	13	8	45
Sales	22	21	6	4	73
Administative support, clerks	47	44	13	7	47
Precision production, craft, repair	22	19	7	3	75
Machine operator, assembler, insp	18	14	6	2	81
Transportation, material moving	26	22	9	*	71
Handler, equipt clnr, helpr, laborer	20	17	6	5	78
Service	23	19	6	2	74

* Less than two percent.

(a) Work hours status is as defined by the individual reporting establishment.

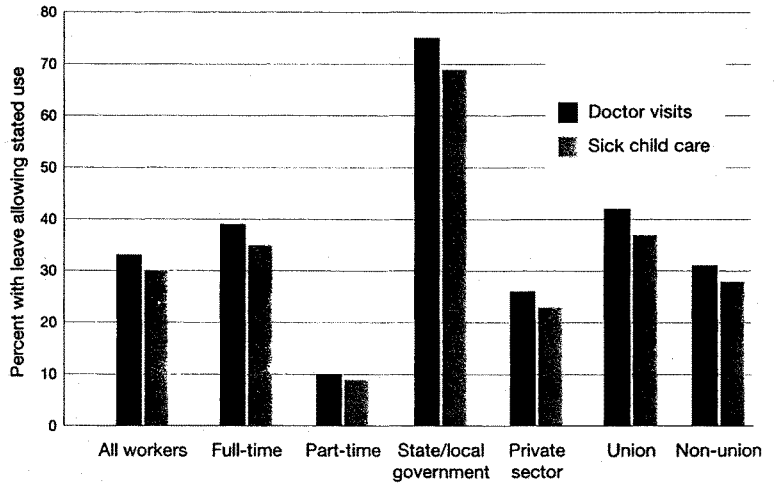
(b) Union includes all workers whose working conditions are collectively bargained.

(c) Includes forestry, fishing, and mining. Data not available for these industries individually due to sample sizes.

Notes: Dataset excludes federal, military, agricultural, household, and self-employed workers. Columns do not sum to 100 percent since sick leave plans may offer multiple uses.

Source: Institute for Women's Policy Research analysis of the 1996-1998 Employee Benefits Surveys.

Figure 3. Percent of workers with paid sick leave usable for doctors' appointments and sick child care, by work hours, sector, and union status, 1996-1998



Notes: Work hours are as defined by the individual reporting establishment. "Union" includes all workers whose working conditions are collectively bargained. Dataset excludes federal, military, agricultural, household, and self-employed workers.
Source: Institute for Women's Policy Research analysis of the 1996-1998 Employee Benefits Surveys.

and professional and business services (36 percent) can take advantage of this benefit as well. Coverage in other industries ranges downward from these levels to accommodation and food services, the industry with the lowest coverage level—five percent.

White-collar occupations have the highest incidence level for this policy, with around half of workers in professional and technical jobs (50 percent), executive, administrative, and managerial positions (49 percent), and administrative support and clerical occupations (47 percent) covered. In all other occupations, coverage is provided to only about one in four or one in five workers.

Caring for Sick Children. Overall, the level of support for workers' family caregiving through the development of paid time off to care for sick children through paid sick leave is very low: only 30 percent of all workers are covered by paid sick leave plans that provide this opportunity. Nearly 86 million workers do not have paid sick child leave.

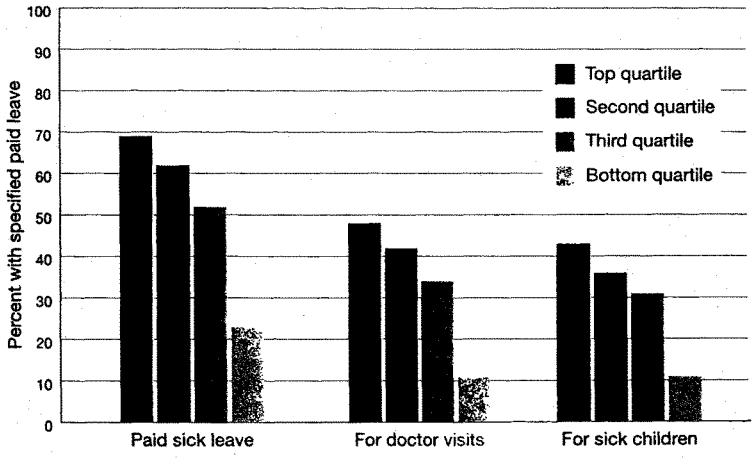
In general, the patterns regarding differences by work hours, between the public and private sector, by union representation, and among industries and occupations are nearly identical to those related to using paid sick leave for doctors' appointments. One in three full-time workers (35 percent) can use paid sick leave to care for sick children, but fewer than one in ten part-timers (9 percent) has this benefit. Workers employed in the public sector are much more likely to have paid sick leave with this allowance—seven in ten (69 percent)—compared to private-sector workers (23 percent, or only two in ten). Unionization matters in accessing paid sick leave to care for sick chil-

dren, with more than one-third of union members (37 percent) versus only 28 percent of non-union workers covered by such a policy.

Two industries stand out as having the most comprehensive integration of sick-child care into paid sick leave: state and local government and educational services, each of which allows two-thirds of its workforce to use paid sick leave to stay home with sick children (69 and 68 percent, respectively). In two others—financial activities and utilities—nearly half of workers have this benefit (47 and 45 percent). Between about a quarter and a third of workers in several other industries can use their paid sick leave to care for kids: natural resources (40 percent), health care and social assistance (36 percent), information (32 percent), professional and business services (31 percent), and wholesale (28 percent) and retail (22 percent) trade. A large number of industries offer very minimal use of paid sick leave for sick-child care, covering only one in five, or fewer, workers: art, entertainment, and recreation (20 percent), transportation and warehousing (19 percent), durable manufacturing (18 percent), construction and "other" service (14 percent each), and, barely registering on this measure, non-durable manufacturing and accommodation and food service (9 and 4 percent, respectively).

As with paid sick leave itself, the level of variation among occupations in approval of using paid sick leave for sick-child care is lower than among industries. No single occupation reaches the level of adequacy seen in some industries; in fact, in no occupation do more than half of all workers have this benefit. Again, the white-collar occupations — professional and technical, executive, administrative, and managerial, and administrative support and clerical — offer this leave to the largest percent of workers (47, 44, and 44 percent, respectively). The other occupations are all fairly similar in the adequacy of their sick-leave coverage, providing paid sick child care through paid sick leave to about one in five workers (22 percent in transportation

Figure 4. Percent of workers with paid sick leave, doctor visit leave, and sick child leave, by wage quartile, 1996-1998



Note: Dataset excludes federal, military, agricultural, household, and self-employed workers.
Source: Institute for Women's Policy Research analysis of the 1996-1998 Employee Benefits Surveys and various quarters of the Employmnet Cost Index, 1995-1998.

Table 4. Percent and number of workers with paid sick leave and with plans allowing selected uses, by wage quartile, 1996-1998

	Wage quartile:			
	Top	Second	Third	Bottom
With paid sick leave				
All				
Percent	69	62	52	23
Number (millions) (a)	21.0	18.9	15.9	7.0
By industry:				
Natural resources (b)	74	44	57	n/a
Construction	34	25	16	11
Manufacturing, durable	50	34	28	23
Manufacturing, non-durable	49	42	32	25
Wholesale trade	66	66	56	28
Retail trade	53	68	56	29
Transportation and warehousing	83	56	44	14
Utilities	88	92	80	n/a
Information	65	75	73	24
Financial activities	74	79	77	37
Professional and business services	67	68	48	20
Educational services	93	88	82	68
Health care and social assistance	63	66	59	45
Art, entertainment, recreation	56	53	54	13
Accommodation and food service	68	51	31	8
Other service	53	51	30	15
Government	85	94	84	43
With plan allowing use for:				
Other	54	47	39	14
Doctors' appointments	48	42	34	11
Sick children	43	36	31	11
Personal	12	11	11	4
None	46	54	61	86
With no paid sick leave				
Percent	31	38	48	77
Number (millions) (a)	9.5	11.6	14.6	23.5
Sample size	11,012	9,441	7,277	5,056
Population (millions) (a)	30.5	30.5	30.5	30.5

n/a: Sample size too small to allow calculation of this incidence rate.
(a) Based on 2003 workforce.
(b) Includes forestry, fishing, and mining. Data not available for these industries individually due to sample sizes.
(c) Includes funeral, data not shown separately, and other leave types not surveyed individually.
Notes: Dataset excludes federal, military, agricultural, household, and self-employed workers.
Source: Institute for Women's Policy Research analysis of the 1996-1998 Employee Benefits Surveys and various quarters of the Employment Cost Index, 1995-1998.

and warehousing; 21 in sales; 19 in both precision production, craft, and repair and service; 17 in handler, equipment cleaner, helper, and laborer; and 14 in machine operators, assemblers, and inspectors).

Using Sick Leave for Other Purposes. A small portion of the workforce (9 percent) is permitted to take care of personal business while receiving pay through a sick leave policy, while fewer still (five

percent) have other specific allowances for use of paid sick leave.

Nearly two-thirds of all workers in the study (63 percent) either have no paid sick leave or are covered by policies that may be used only for workers' own health needs.

Differences in Paid Sick Leave Adequacy by Wage Level. Access to paid sick leave is largely restricted to workers in the top three wage quartiles. [10] Those in the highest wage quartile are three times as likely to have paid sick leave as workers in the bottom wage quartile (coverage rates are 69 and 23 percent, respectively; Figure 4 and Table 4). And rather than declining at a steady rate from one quartile to another, the incidence of paid sick leave is only slightly lower for workers in the second quartile than in the top (62); coverage for those in the third quarter is distinctly lower (52 percent); and then the rate drops precipitously for workers in the bottom quartile.

This pattern is repeated within almost every industry. Construction is an exception: access to paid sick leave is very low for workers in every wage quartile, although the coverage rate is three times higher for workers in the top wage quartile (34 percent) as compared to those in the bottom quartile (11 percent). Both durable and non-durable manufacturing exhibit a fairly even decline in paid sick leave coverage from each wage quartile to the next, with those in the top quartile about twice as likely as those in the bottom to participate in a paid sick leave plan.

In many industries, workers in the bottom wage quartile are virtually isolated in their own low-quality labor market, while workers in the other three wage quartiles share relatively similar access to paid sick leave. For instance, in art, entertainment, and recreation, paid sick leave is provided to 56 percent of workers in the top wage quartile, 53 percent of those in the second quartile, and 54 percent of those in the third quartile, but to only 13 percent of workers in the bottom wage quartile (about one in eight). Similar conditions exist in both wholesale and retail trade, information, financial activities, educational services, and state and local government. In others, paid sick leave coverage is provided at similar rates to workers in the top two wage quartiles, with the incidence rate dropping off for those in the third quartile and falling further yet for those in the bottom (professional and business services, health care and social services, accommodation and food service, and other service).

Only about one in every ten low-wage workers is allowed to use paid sick leave to stay home with sick children (11 percent), although more than four in every ten workers in the top wage quartile enjoy this benefit (43 percent). The disparity in incidence rates of policies allowing use of paid sick leave for doctors' appointments is similar (48 percent of workers in the top quartile, but only 11 percent of those in the bottom, have this right). Use of paid sick leave to conduct personal business is permitted for about one in every eight workers in the top three wage quartiles, but only one of every twenty-five workers in the bottom quartile.

Low-Wage Workers and Paid Sick Leave

Low-wage workers clearly face a health crisis in the form of inadequate paid sick leave. With fewer than one in four low-wage workers covered by paid sick leave, millions—nearly 24 million—are left with no good option when the inevitable happens and they catch the flu, or a chronic medical problem flares up. Poor workers and those receiving welfare are much less likely to have *any* leave than other workers—only 46 percent of the poor and 41 percent of welfare recipients do (Ross Phillips 2004)—and low-income workers are also disproportionately excluded from unpaid, job-protected leave under the Family and Medical Leave Act (Cantor et al. 2001).

Paid Sick Leave and Women

To a large degree, the patterns of paid sick leave coverage revealed in this analysis are strikingly congruent with women's employment patterns. Paid leave is rarely available to low-wage workers—and women are the majority of this group (60 percent of minimum-wage workers are women; Mishel, Bernstein, and Boushey 2003). Workers in the accommodation and food service industry have virtually no paid sick leave—and the majority of workers in this industry are women (53 percent; U.S. Bureau of Labor Statistics 2004a). Almost all part-time workers are excluded from both paid sick leave and paid sick family leave—and three of every five part-time workers are women (U.S. Bureau of Labor Statistics 2004a).

The burden of inadequate paid sick leave and paid sick family leave falls heaviest on mothers. Given current norms of caregiving, they are more likely to need to stay home with a sick family member than fathers, yet mothers are less likely than

fathers to have any paid time off, and those who do have some paid leave have fewer weeks of paid time off than dads (Ross Phillips 2004). And because women earn less than men, and mothers are among the younger employed women, in workplaces where leave arrangements are negotiated between individual workers and supervisors, mothers with the fewest financial resources to sustain them during periods of unpaid sick leave (or, in the worst case, after being fired) face the greatest difficulty in winning adequate paid time off (Glass and Estes 1997).

Summary and Policy Recommendations

All workers are subject to occasional health deficits that require time off work, and all need time for routine medical care. Those responsible for the health of children or other family members must also have the opportunity to stay at home when necessary or accompany family members to their medical appointments. Yet many millions of workers do not have paid sick leave for their own health needs, and even more lack paid sick time to care for their families. Despite the myriad problems caused by inadequate paid sick leave, nearly half of all workers have none. Part-time and low-wage workers have very little access to paid sick leave and paid sick family leave. Workers in the private sector have worse access to paid sick leave benefits than public-sector workers. Union membership increases the likelihood of having paid sick leave. A few industries, including the two most highly unionized (utilities and state and local government), have relatively well-developed paid sick leave policies, but variation among industries is extremely high. Paid sick leave is much more available to white-collar workers than to others.

Our system of voluntary paid sick leave provision is clearly failing to reach tens of millions of workers whose health depends on their being able to recuperate at home when they become ill. Co-workers and employers also suffer when workers show up sick at the office, as contagion reduces productivity and increases absence. Sick leave policies are failing to provide the paid time off that caregivers need, leading to loss of jobs and income and worse health outcomes for children. And a closer look at paid sick leave coverage patterns reveals great inequities, with the least support going to the most vulnerable: part-time and low-wage workers.

Paid time off policies need to be modified in order to increase the adequacy of this critical employment benefit and work support. Policies and actions such as the following would reduce the costs of not having paid sick leave, while improving employment and health outcomes:

- Expand existing paid sick leave programs; add wage replacement to unpaid sick leave policies. Every worker should have paid sick leave.
- Enable workers to use their paid sick leave to care for their sick loved ones.
- Allow use of paid sick leave for workers' and family members' routine medical care.
- Extend paid sick leave programs to cover workers during their probationary period.
- Change corporate cultures to make sure workers feel comfortable using their paid sick leave time, to promote workers' own health outcomes, avoid spreading diseases to co-workers, and minimize employers' overall absence rates.
- Expand options for parents with sick children through supporting sick-child care centers, so parents have the choice to stay at work while ensuring that their children's health needs are met.
- Allow greater flexibility in work schedules and at-home work arrangements, so workers can adapt their hours at work to fit the demands of their health-related caregiving responsibilities.

Healthy workers can contribute their maximum work effort on the job, boosting employers' productivity, output, and efficiency. Paid sick leave is an essential health care policy that supports workers' well-being while preventing contagion and work loss among co-workers. Workplace adjustments to support the critical efforts of workers to safeguard their families' health are also crucial.

Everyone benefits from allowing workers to regain their good health—not only workers themselves, but employers, co-workers, kids, other family members, and society at large. Paid sick leave is a prescription for a productive workforce, successful employers, and healthy families.

Appendix: The BLS Dataset

The U.S. Department of Labor's Bureau of Labor Statistics (BLS) began publishing survey data on employee benefits in 1955. Periodic expansions of the sample frame culminated with the 1990s versions of the Employee Benefits Survey (EBS), an annual survey of establishments[11] on employee benefits available to non-agricultural wage and salary workers outside the federal and private household sectors.[12] The EBS collected data about a wide range of paid time off, health care, retirement, and other benefits for which employers incurred costs.[13] A sample of establishments was surveyed, with each reporting on benefit coverage of incumbents in a sample of job positions. From 1990 to 1998, each year's EBS focused on one set of employers: either state and local governments, small private establishments (those with fewer than 100 workers), or medium and large private establishments (Blostin 1999).[14] Neither demographic data such as sex and level of educational attainment nor wage data were collected in the EBS. The EBS instruments were fielded throughout the year and reflected benefit coverage as of the day of the survey site visit.

To explore benefit adequacy by wage level for this research project, wage data from the BLS Employment Cost Index (ECI) were merged with the EBS data.[15] Prior to development of the National Compensation Survey, which now supercedes it, the ECI was a quarterly BLS establishment survey designed to document trends in employers' costs for compensation, including wages and benefits. Employers were selected for participation in the EBS using the ECI sample frame.

To assess the adequacy of employers' paid sick leave policies for all employer groups, this analysis combines data from the merged EBS and ECI surveys for the 1996 EBS survey of small private establishments, the 1997 survey of medium and large private establishments, and the 1998 survey of state and local governments into a single dataset. The final dataset contains data for 54,247 workers. Wage data from the ECI were converted to December 1998 dollars using the CPI-U-RS. Sick leave coverage statistics were calculated using the weight from a subfile of the EBS (the INCID file).

Endnotes

[1] Research in other countries has failed to find a similar effect of young children on mothers' absence rate (Mastekaasa 2000, VandenHeuvel and Wooden 1995), possibly because these countries have much more substantial paid maternity leave policies than the United States., so more mothers are on leave when their children experience the frequent medical needs of infancy.

[2] The law applies to workers in all public agencies and in private-sector establishments employing at least 50 workers within a 75-mile radius. Eligibility standards require that workers have been employed by a covered employer for 12 months and have performed at least 1,250 hours of work for that employer in the 12 months preceding the leave. Leave may be taken for childbirth; to care for a newborn child, newly placed adoptive or foster child, or a seriously ill spouse, child, or parent; or for an employee's own serious health condition. Leave may be taken intermittently when medically necessary. Employers must continue to provide existing group health insurance coverage for employees who are on FMLA leave, under the same conditions as if the employee were not on leave (Commission on Family and Medical Leave 1996). While the law provides for job protection it does not require employers to offer paid leave.

[3] Single mothers have lower sick leave coverage rates than other mothers, making their children's higher absence rates even more difficult to manage (Heymann, Earle, and Egleston 1996).

[4] Eligible workers may continue health insurance for some period after job termination, if they can afford the premium payments (U.S. Department of Labor n.d.).

[5] For this study, low-income was defined as less than 200 percent of the federal poverty line, and poor as less than 100 percent of that threshold.

[6] The surveys report whether workers participate in the stated benefit programs—that is, they represent situations where workers are both offered and take up the benefit (Wiatrowski 1996).

[7] These exclusions represent approximately 10 percent of the total workforce.

[8] Data on coverage of federal employees are not available from this dataset, but the U.S. Office of Personnel Management lists paid sick leave as a standard benefit for federal workers. The leave may be used to care for family members (U.S. Office of Personnel Management n.d.).

[9] In addition, some workers may have paid time off for illness under union programs that are not reflected in the Department of Labor survey.

[10] The wage quartiles are defined as: 1996: top, $17.54 and above; second, $10.80 to $17.53; third, $7.28 to $10.79; bottom, below $7.28; 1997: top, $17.66 and above; second, $11.03 to $17.65; third, $7.49 to $11.02; bottom, below $7.49; and 1998: top, $18.35 and above; second, $11.45 to $18.34; third, $7.68 to $11.44; bottom, below $7.68; all in December 1998 dollars.

[11] An establishment is a single employment location; one firm may comprise multiple establishments.

[12] In the 1990s, the EBS covered 96 percent of all civilian non-federal non-agricultural workers.

[13] Employee-financed benefits are not reflected in the EBS.

[14] Beginning in 1999, the BLS has moved toward full implementation of a consolidated annual survey, the National Compensation Survey, which samples both public (state and local) and private establishments of all sizes, collecting data on benefits as well as the wage and compensation cost data that was previously part of the Employment Cost Index, the Employer Costs for Employee Compensation survey, and the Occupational Compensation Survey (Blostin 1999).

[15] Data on paid sick leave were contained in two workfiles developed by the BLS from the EBS: INCID and SCKLV. These were first merged, using the establishment identification number, an occupation identifier, and the leave plan number as match variables. The employer and occupation variables were then used to combine the EBS and ECI data. Only cases with positive reported hourly wage rates in the ECI were retained. To maximize the sample, EBS data were allowed to seek a match in several previous quarters of ECI data.

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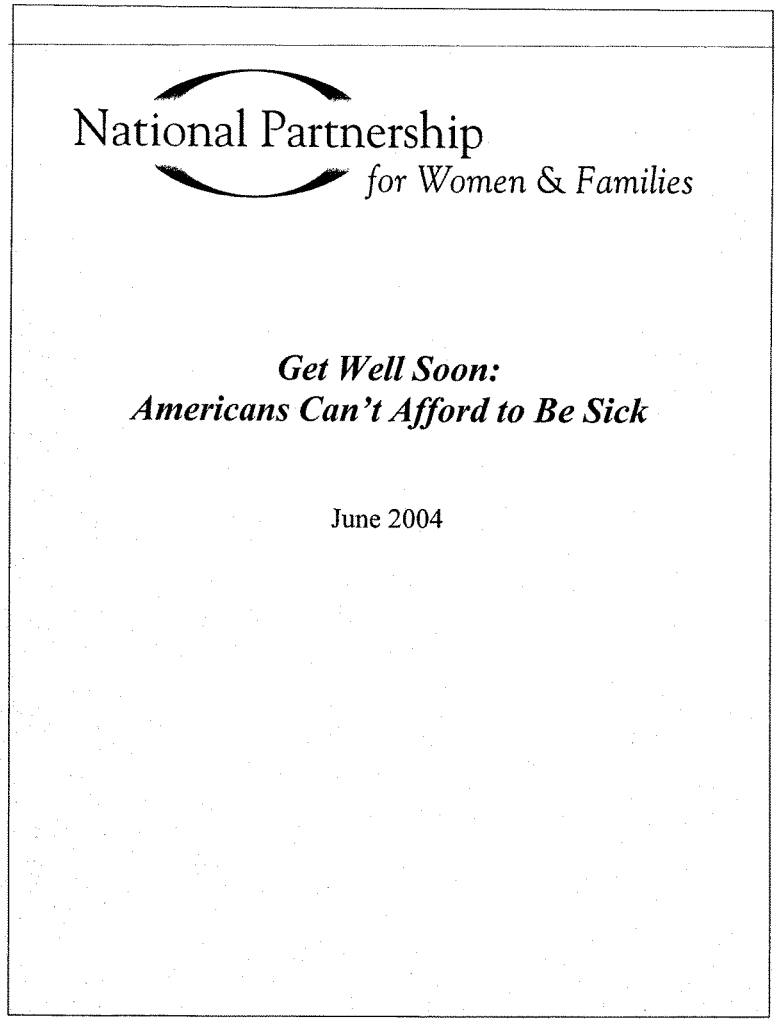

Get Well Soon:
Americans Can't Afford to Be Sick

June 2004

The National Partnership for Women & Families promotes fairness in the workplace, quality health care, and policies that help women and men meet the dual demands of work and family. Working with business, government, unions, nonprofit organizations and the media, the National Partnership is a voice for fairness, a source for solutions, and a force for change. Visit the National Partnership on the web at www.nationalpartnership.org.

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Executive Summary
Get Well Soon: Americans Can't Afford to Be Sick

Humane working conditions assume some paid leave when illness strikes. Yet, millions of workers in the United States are without this most basic benefit. In fact, the U.S. lags far behind the rest of the world in giving workers paid sick leave. Almost half (47 percent)[1] of private sector workers, and 59 million total workers in the U.S., have no paid sick days at all.[2]

A nation that truly values families would allow workers to use their paid sick leave to care for a child or other family member who is ailing. Yet 86 million workers in the U.S. do not have a single paid sick day that can be used to care for sick children.[3]

New research from The Project on Global Working Families at Harvard University finds that 139 nations provide paid leave for short or long term illnesses, and 117 of those nations guarantee their workers a week or more of paid sick days per year. However, no federal law in the United States guarantees a single day of paid sick leave to workers. The federal Family & Medical Leave Act provides only *unpaid* leave for serious illnesses to the approximately 60 percent of the workforce that it covers.

This report is the most comprehensive assessment to date of state and federal measures governing paid sick days. It examines laws, regulations, contractual agreements and other mechanisms that give workers access to paid sick leave.

The findings paint a picture of need and neglect. The failure to provide paid sick days to workers causes profound harm to families. It also results in unnecessary costs to businesses that spend money recruiting and training new workers, when employees already in place could often keep their jobs if some paid sick leave was available to them.

Get Well Soon: Americans Can't Afford to Be Sick finds that not a single state is doing all it should to guarantee paid sick days to employees. Still, promising models are emerging and are explored in this report. All states provide paid sick days to their own employees, but some states are much more generous than others. More and more states are setting an example by allowing workers to use paid sick leave to care for close family members. It is especially encouraging that some states are beginning to govern private sector paid sick leave practices.

California is far ahead of any other state in providing workers with family leave benefits – and yet, even California's paid family leave program does not provide job protection for workers on

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[1] U.S. Department of Labor, Bureau of Labor Statistics, *Employee Benefits in Private Industry, 1999*, http://www.bls.gov.
[2] Vicky Lovell, *No Time to be Sick: Why Everyone Suffers When Workers Don't Have Paid Sick Leave*, Institute for Women's Policy Research, May 2004, p.1.
[3] *Id.*

leave.[4] Hawaii is next, followed by New Jersey, Rhode Island and New York.

Mississippi has the distinction of providing fewer sick leave benefits to state workers than any other state. Louisiana is barely better, followed by Arkansas, Idaho, Indiana, Kansas, Kentucky, Maine, North Carolina, North Dakota, South Dakota, and Wyoming in providing the fewest sick leave benefits for their workers.

The federal government gives its more than 2.7 million workers 13 paid sick days a year – relatively generous compared to the private sector but no better than what many states offer their own employees. And the federal government lags behind several states in that it does not require private employers to provide any paid sick leave.

The National Partnership for Women & Families has designed ***Get Well Soon*** to share information, generate a public conversation, and spur action to make our nation's workplaces more compassionate, healthier and ultimately, more productive.

[4] Individuals covered by the federal Family and Medical Leave Act, or California's laws providing job protection for women on pregnancy leave or some workers on family and medial leave, would receive job protection. These laws do not cover all of the workers who could take advantage of California's paid family and medical leave program.

Get Well Soon: Americans Can't Afford to Be Sick

Introduction

Those who have it take it for granted. Those who don't struggle every time illness strikes.

Paid sick leave is the next frontier in the effort to make our nation's workplaces more worker- and family-friendly. It needs to be. Too many hard-working Americans must choose between a paycheck and recovery when they get the flu, break a bone, or need to care for an ailing child, spouse, or parent.

The numbers point to enormous need. On average workers need about a week of sick leave each year to take care of their own health needs.[1] Workers who have paid sick days do not have to think twice about staying home to recover from the flu or to take a sick child to the doctor. But for almost half of the employees in this country, the choice is much more difficult because it means a day without pay or even the loss of a job or opportunities for advancement. And in most states, workers who are fired as a result of taking sick leave are not eligible for unemployment insurance.[2]

Lack of Sick Leave Benefits In the United States
The statistics on paid sick leave in the U.S. are disturbing:

- Almost half (47 percent) of private sector workers have no paid sick days.[3]
- 59 million workers (public and private) have no paid sick days.[4]
- 86 million workers (public and private) do not have paid sick days to care for sick kids.[5]

Sick Children
Personal illness is not the only reason workers need paid sick leave. Caregiving responsibilities can add significantly to the need. In 78 percent of American families, both parents work.[6] Every parent knows that children get sick. In fact, children age five to 17 average more than three days per year out of school due to health problems.[7] If the parents of these children do not have paid sick days, they must choose between leaving a sick child home alone, or missing pay and possibly putting the family's economic stability at risk.

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[1] Vicky Lovell, *No Time to be Sick: Why Everyone Suffers When Workers Don't Have Paid Sick Leave,* Institute for Women's Policy Research, May 2004, p.3.
[2] Rebecca Smith, Rick McHugh, Andres Stettner, and Nancy Segal, *Between a Rock and a Hard Place: Confronting the Failure of State Unemployment Insurance Systems to Serve Women and Working Families,* National Employment Law Project, July 2003, p.13.
[3] U.S. Department of Labor, Bureau of Labor Statistics, *Employee Benefits in Private Industry, 1999,* http://www.bls.gov.
[4] Lovell, *No Time to be Sick,* p.1.
[5] *Id.*
[6] Families and Work Institute, *Highlights of the 2002 National Study of the Changing Workforce,* 2004, p.14, http://www.familiesandwork.org.
[7] Lovell, *No Time to be Sick,* p.3.

If the parent cannot afford to stay home, children may suffer. One study found that 41 percent of parents said their working conditions had negatively affected their children's health in ways that ranged from a child missing a needed appointment with a doctor to a child failing to receive adequate early care which caused an illness or condition to worsen.[8]

The opposite is true as well. Children benefit when their parents have paid sick leave. The presence of parents has been shown to reduce the duration of children's hospital stays by 31 percent. And when parents are involved in children's care, children recover more rapidly from outpatient procedures.[9]

Elder Care

Workers have responsibilities beyond sick children. The number of employees who need time off to care for sick spouses or elderly parents is growing. According to a 2002 study, more than a third of Americans (35 percent) had significant elder care responsibilities in the past year.[10] More than one-third of workers with these elder care obligations were forced to reduce their work hours or take time off to provide needed care.[11] Many suffered financially as a result.

Lower-Income Workers

Workers at the bottom of the economic ladder are least likely to have access to paid leave. According to Dr. Jody Heymann, a researcher at Harvard University, 76 percent of low-wage workers have no paid sick leave.[12] A recent Urban Institute study found that 41 percent of working parents with incomes below 200 percent of the federal poverty line have no paid leave of any kind – no paid sick leave, no paid vacation, and no paid personal days off.[13]

Workers who do have paid sick days often cannot use it to care for a sick family member. In one study, 34 percent of parents reported that caring for their sick children led to difficulties at work; 12 percent said it led to lost pay; and 13 percent to loss of promotions or jobs.[14]

The problem is particularly acute for working women, who in most families are responsible for meeting the majority of family caregiving needs. Half of working mothers (49 percent) report that they do not get paid when they stay home to care for a sick child.[15]

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[8] Jody Heymann, *The Widening Gap: Why America's Working Families are in Jeopardy and What Can Be Done About It*, Basic Books, 2000, p. 62.
[9] Jody Heymann, Sara Toomey, and Frank Furstenberg, "Working Parents: What Factors Are Involved in Their Ability to Take Time Off From Work When Their Children Are Sick?" *Archives of Pediatrics and Adolescent Medicine*, vol. 153, August 1999.
[10] Families and Work Institute, *Highlights of the 2002 National Study of the Changing Workforce*, 2004, p.29, http://www.familiesandwork.org.
[11] *Id.at p.30.*
[12] Heymann, *The Widening Gap*, p.45.
[13] Katherin Ross Phillips, *Getting Time Off: Access to Leave among Working Parents*, The Urban Institute, April 2004, http://www.urban.org.
[14] Heymann, *The Widening Gap*, p.65.
[15] Kaiser Family Foundation, "Women, Work and Family Health: A Balancing Act," Issue Brief, April 2003, http://www.kff.org/content/2003/3336/Balancing_Act_IssueBrief.pdf.

Paid Sick Days Make Good Business Sense

Paid sick leave is not just good for families with children. Employees with paid sick leave are less likely to come to work when ill and less likely to infect their colleagues. In fact, 44 percent of corporate human resource executives say that "presenteeism" – employees coming to work when they are ill – is a problem in their companies.[16] A recent study from the Cornell University Institute for Health and Productivity Studies found that "presenteeism" costs employers an average of $255 per employee per year, and that on-the-job productivity losses from "presenteeism" may be as high as 61 percent of an employee's total medical and lost productivity costs.[17] That exceeds the costs of absenteeism and medical and disability benefits.[18]

Paid sick leave is good for business in other ways. According to one statistical model, offering workers the option to take time off when a family member is sick improves profits.[19] Employers who provide paid leave benefits to their employees see greater retention: 94 percent of leave-takers who are fully paid (compared to 76 percent of those who are not paid) return to their employers after taking leave.[20] In fact, a number of studies have found that businesses that provide paid leave for workers benefit from higher productivity and morale, lower turnover and training costs, and reduced absenteeism.[21] In most cases, these benefits more than make up for the direct costs of providing paid leave.[22]

Paid sick leave matters to Americans. A 2002 study by Office Team, a California-based staffing services firm, found that most workers ranked work and family balance as their top concern for the year – above competitive salary and job security.[23] Being able to take time off to recover from an illness or care for a sick child or spouse is fundamental to being able to balance work and family responsibilities.

Is our nation beginning to solve the problem of inadequate paid sick leave? Are public and private employers adopting more humane policies in this regard? Are we putting laws and policies in place that will give more workers access to paid sick leave? Are we doing what we should to support parents with sick children, workers with ailing spouses, employees who need to care for ill parents? This report explores those questions in depth, providing the most comprehensive information ever developed on paid sick leave laws in the United States.

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[16] CCH Incorporated, *2003 CCH Unscheduled Absence Survey*, October 2003, http://www.cch.com/press/news/2003/20031022h.asp.
[17] "Call in sick, save the boss money," April 22, 2004, http://www.cnn.com/2004/HEALTH/04/22/sick.call.ap.
[18] Cornell News Press Release, April 20, 2004, http://www.cepr.cornell.edu.
[19] Christine Siegwarth Meyer, Swati Mukerjee, and Ann Sestero, "Work-Family Benefits: Which Ones Maximize Profits?" *Journal of Managerial Issues*, vol. 13, no. 1, Spring 2001, p. 39.
[20] Commission on Family and Medical Leave, *A Workable Balance: Report to Congress on Family and Medical Leave Policies*, 1996, p. 114.
[21] Marilyn P. Watkins, *The Case for Minimum Paid Leave for American Workers*, Economic Opportunity Institute, January 2004, p.9.
[22] *Id.*
[23] *Employee Benefits News*, "Benefit Priorities Shift as Families Demand More Time," August 1, 2002.

Sadly, the answer to most of those questions is "no." ***Get Well Soon*** documents inadequate laws and unmet needs. It is designed to focus the spotlight on a major problem affecting millions of Americans and, its authors hope, to serve as a catalyst for real change.

Methodology

This report focuses on access to paid sick leave, examining how each state, the District of Columbia, and the federal government provide or guarantee access to paid sick days for workers in the public and private sectors. Specifically, it answers the following questions:

Private Sector

- Does the state guarantee all workers access to paid sick days?
- Does the state have a program to provide private sector workers with paid family leave to care for sick family members?
- Does the state have a program to provide private sector workers with medical leave benefits to recover from their own short-term disability?
- Does the state require private employers to let workers use their paid sick days to care for family members?

State Employees

- How many paid sick days does a state provide to its own employees each year?[24]
- How many paid personal days, that can be used in addition to sick days to care for one's self or a sick family member, does the state provide to its own employees each year?
- Can state employees use their sick days to care for family members?
- Does the state have a sick leave pool that allows state employees to apply for additional paid sick days in times of need?
- Does the state have a direct donation program that permits a state employee to donate unused sick or annual leave to a co-worker in need of additional sick days?
- Does the state make short-term disability insurance available to state employees?

To answer these questions, the authors consulted a variety of sources:

- As part of its Campaign for Paid Leave Benefits, the National Partnership for Women & Families tracks state developments on paid family and medical leave laws and publishes the information annually in a State Round-Up. For information on what states guarantee to private sector workers, the National Partnership relied on the most recent version (2003) of its State Round-Up, which reviews state activities regarding access to paid family leave benefits and paid sick days. The authors also consulted relevant state statutes and regulations and state websites.
- For information on what benefits each of the 50 states provides to state employees, the authors primarily relied on the *2004 State Employee Benefits Survey* published by Workplace Economics, Inc. In cases where the National Partnership's State Round-Up included a state law governing state employees, the authors consulted the relevant state statute and/or regulation.

[24] Authors relied on number of paid sick days given in the first year of employment, as most states do not tie the amount of sick leave to service.

- For information on what benefits the District of Columbia provides to city employees, authors consulted the D.C. Personnel Manual available to the public via the D.C. public library system and the D.C. government.

- Authors reviewed federal Office of Personnel Management (OPM) materials available on the Internet, and spoke with officials at the OPM to determine federal sick leave policies.

Authors awarded points to each state based on the programs made available to private and public employees. As most employees work in the private sector, the point system favors laws that provide protection and benefits to private sector employees.

Sadly, not a single state or federal law in the country guarantees workers the right to job protected paid sick leave. America's families desperately need policies that guarantee access to this critical work/life support.

The good news is that some states are setting an example. Several have laws that govern access to paid leave that can be used for one's own illness or to care for a family member. And all states offer their own employees paid sick leave benefits, although some states are much more generous than others.

Laws Governing Private Sector Employees

Only a handful of states have adopted laws that give private sector employees access to paid sick leave through paid family and or medical leave, or guarantee employees the right to use their employer-provided paid sick leave to care for a sick family member. Authors assigned:

- 25 points to states that guarantee all workers access to job-protected paid sick days. None do.

- 20 points to states that have programs in place to give workers family leave benefits to care for sick family members. Beginning July 1, 2004, 13 million California families will be eligible for up to six weeks of family leave benefits at 55 percent of salary to care for a seriously ill family member or newborn/newly adopted child. The program is funded by employee payroll deductions. The program does not provide job protection for employees on leave, although an employee on family leave may have job protection through the federal Family & Medical Leave Act or the California state Family and Medical Leave Law.

- 20 points to states that have programs in place to give workers medical leave benefits to recover from their own short-term disability. Five states – California, Hawaii, New Jersey, New York, and Rhode Island[25] – have enacted state-wide programs to provide paid leave for employees needing to take time off from their jobs due to illnesses unrelated to work (including pregnancy and childbirth-related conditions). The programs do not provide job protection for employees on leave, but are instead similar to unemployment insurance, replacing a portion of workers' lost earnings during the period of disability. An employee on short-term disability leave may have job protection

[25] Puerto Rico also has a Short-Term Disability program.

through the federal Family & Medical Leave Act or a similar state statute. Each state's program is unique, but generally requires employers either to offer this coverage to employees or establish a state-administered disability insurance fund. The programs are funded either through employee or employer contributions, or a combination of both.

- 15 points to states that require private employers to let workers use their paid sick days to care for family members. California, Connecticut, Hawaii, Minnesota, and Washington state have laws that mandate this flexible use of sick days.

Benefits Provided to State Employees

Authors assigned:

- One point for each paid sick day, over seven, that a state provides to its own employees each year.[26] Iowa and West Virginia lead the nation, offering state employees 18 sick days a year. State employees in Colorado fare the worst, receiving only 10 paid sick days per year.

- One point for each paid personal day that a state provides to its own employees, which can be used in addition to sick days to care for oneself or a sick family member. Nineteen states offer paid personal leave in addition to paid sick leave. Maryland offers the most personal leave – six days. State employees in Maryland are eligible for a total of 21 days of paid sick and personal leave each year. Following closely behind, employees in Connecticut, Iowa, Massachusetts, New Jersey, and West Virginia are eligible for 18 days of paid sick and/or personal days. The median length of combined sick and/or personal days is 14 days. The federal government falls below the state median as it provides federal employees with 13 days of sick leave and no personal leave.

- Three points if the state allows state employees to use their sick leave to care for family members – two points if this benefit is only available to some state employees. Forty-eight states, the District of Columbia, and the federal government allow state employees to use their sick leave to care for family members. Louisiana is the only state that neither provides paid sick nor personal leave to care for sick family members. In Virginia employees hired prior to 1999 can use their sick leave for this purpose. Virginia employees hired since 1999 can only use their personal leave – and not their sick leave – to care for sick family members.

- Five points if the state has a sick leave pool that allows state employees to apply for additional paid sick days in times of need – three points if this benefit is only available to some state employees. Eighteen states – as well as the District of Columbia and the federal government – have created sick leave pools that employees who have exhausted their paid leave can obtain additional leave. These pools are usually limited to catastrophic illness and/or when an employee has used all of his or her own leave. Arkansas, Connecticut, Delaware, Florida, Illinois, Louisiana, Maryland, Massachusetts,

[26] Only Hawaii, Kentucky, Louisiana, Mississippi, Nebraska, Vermont, Virginia, the District of Columbia, and the federal government tie sick leave to years of service. As a result, the authors awarded points based on the first year of service.

Missouri, Montana, Nevada, Ohio, Rhode Island, South Carolina, Tennessee, Texas, Utah, Vermont, the District of Columbia, and the federal government have sick leave pools.

- Five points if the state has a direct donation program that permits a state employee to donate unused sick or annual leave to a co-worker in need of additional sick days. Three points if this benefit is only available to some state employees. Twenty-two states either allow workers to donate additional paid leave to co-workers in need who have exhausted their sick leave or have a program to grant additional leave to workers who exhaust their leave. Alabama, Alaska, Arizona, California, Colorado, Delaware, Hawaii, Iowa, Kansas, Kentucky, Montana, Nebraska, New Jersey, New Mexico, New York, North Dakota, Oklahoma, Pennsylvania, Tennessee, Virginia, Washington, Wyoming, and the federal government have direct donation programs. Although they do not have direct donation programs, both Georgia and New Hampshire received points because these states have alternative programs that allow workers who exhaust their sick leave to receive additional paid leave. Georgia received three points for its program that grants workers additional paid leave on a case-by-case basis, and New Hampshire received five points for its supplemental sick leave plan.

- Five points if the state makes short-term disability insurance available to state employees. Three points if this benefit is only available to some state employees. Twenty-nine states and the District of Columbia make short-term disability insurance available to state employees. Alabama, Alaska, Arizona, California, Colorado, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Massachusetts, Michigan, Minnesota, Montana, Nebraska, New Jersey, New Mexico, New York, North Carolina, Ohio, Oklahoma, Oregon, Rhode Island, Texas, Utah, Virginia, West Virginia, Wisconsin, and the District of Columbia either provide or make short-term disability insurance available to their employees.

STATE REPORT CARD

A

No state provides enough benefits to merit a grade of "A".

B+

California

B

Hawaii

B-

New Jersey
New York
Rhode Island

C+

Connecticut
Minnesota
Washington

C

Alaska
Delaware
Illinois
Maryland
Massachusetts
Montana
Oklahoma
Wisconsin

C-

Alabama
District of Columbia
Federal Government
Georgia
Iowa
New Mexico
Ohio
West Virginia

D+

Arizona
Nebraska
Tennessee
Texas
Utah
Virginia

D

Colorado
Florida
Michigan
Missouri
Nevada
New Hampshire
Oregon
Pennsylvania
South Carolina
Vermont

D-

Arkansas
Idaho
Indiana
Kansas
Kentucky
Maine
North Carolina
North Dakota
South Dakota
Wyoming

F

Louisiana
Mississippi

Chart: State-by-State Summary of Benefits (in alphabetical order)

	State guarantees private sector workers access to paid leave	State provides private sector workers with paid leave to care for a sick family member	State provides private sector workers with paid leave for worker's short-term disability	State requires private employers to allow workers to use paid leave to care for family members	# of paid sick days provided to state employees[1]	# of paid personal days provided to state employees	State employees can use sick/personal leave to care for family members	State employees can access sick leave pool	State employees can take advantage of direct donation program	State employees offered short-term disability insurance
Alabama (C-)					13	1	✓		✓	✓
Alaska (C)					15		✓		✓	✓
Arizona (D+)					12		✓		✓	✓
Arkansas (D-)					12		✓	✓		
California (B+)		✓	✓	✓	12	1	✓		✓	✓
Colorado (D)					10		✓		✓	✓
Connecticut (C+)				✓	15	3	✓	✓		
Delaware (C)					15		✓	✓	✓	
Florida (D)					13		✓	✓[2]		✓
Georgia (C-)					15		✓		✓[3]	✓
Hawaii (B)			✓	✓	15[4]		✓		✓	✓
Idaho (D-)					12		✓			✓
Illinois (C)					12	3	✓	✓		✓
Indiana (D-)					9	3	✓			✓
Iowa (C-)					18		✓		✓	
Kansas (D-)					12		✓		✓	
Kentucky (D-)					12		✓		✓	
Louisiana (F)					12			✓		

[1] Only Hawaii, Kentucky, Louisiana, Mississippi, Nebraska, Vermont, Virginia, the District of Columbia, and the federal government tie sick leave to years of service.
[2] Florida agencies can establish sick leave pools or other methods to provide additional sick leave to employees in need.
[3] Georgia provides additional leave on a case-by-case basis.
[4] 21 days if hired before 7/2/01.

	State guarantees private sector workers access to paid leave	State provides private sector workers with paid leave to care for a sick family member	State provides private sector workers with paid leave for worker's short-term disability	State requires private employers to allow workers to use paid leave to care for family members	# of paid sick days provided to state employees	# of paid personal days provided to state employees	State employees can use sick/personal leave to care for family members	State employees can access sick leave pool	State employees can take advantage of direct donation program	State employees offered short-term disability insurance
Maine (D-)					12	2	✓			
Maryland (C)					15	6	✓	✓		
Massachusetts (C)					15	3[5]	✓	✓		✓
Michigan (D)					13	2	✓			✓
Minnesota (C+)				✓	13		✓			✓
Mississippi (F)					12[6]		✓			
Missouri (D)					15		✓	✓		
Montana (C)					12		✓	✓	✓	✓
Nebraska (D+)					12		✓		✓	✓
Nevada (D)					15		✓	✓		
New Hampshire (D)					15		✓		✓[7]	
New Jersey (B-)			✓		15	3	✓		✓	✓
New Mexico (C-)					12	1	✓		✓	✓
New York (B-)			✓		8[8]	5	✓		✓	✓
North Carolina (D-)					12		✓			✓
North Dakota (D-)					12		✓		✓	
Ohio (C-)					10	4[9]	✓	✓		✓
Oklahoma (C)					15		✓		✓	✓

[5] Massachusetts state police receive 5 days of personal leave as a result of a collective bargaining agreement.
[6] Sick leave accrual rate drops after 3 years: after 3 years state employees accrue 10.5 days/year; after 8 years employees accrue 9 days/year; after 15 years employees accrue 7.5 days/year.
[7] New Hampshire has a supplemental sick leave plan for workers who exhaust leave.
[8] Depending on bargaining units and the date of the employee's hire, New York provides 8, 10 or 13 days of sick leave to state employees.
[9] Depending on bargaining unit, Ohio provides 3-5 days of personal leave to state employees.

	State guarantees private sector workers access to paid leave	State provides private sector workers with paid leave to care for a sick family member	State provides private sector workers with paid leave for worker's short-term disability	State requires private employers to allow workers to use paid leave to care for family members	# of paid sick days provided to state employees	# of paid personal days provided to state employees	State employees can use sick/personal leave to care for family members	State employees have access to sick Leave pool	State employees can take advantage of direct donation program	State employees offered short-term disability insurance
Oregon (D)					12	2	✓			✓
Pennsylvania (D)					13	1[10]	✓		✓	
Rhode Island (B-)			✓		13	4	✓	✓		✓
South Carolina (D)					15		✓	✓		
South Dakota (D-)					14		✓			
Tennessee (D+)					12		✓	✓	✓	
Texas (D+)					12		✓	✓		✓
Utah (D+)					13		✓	✓[11]		✓
Vermont (D)					12	✓[12]	✓	✓		
Virginia (D+)					8[13]	4[14]	✓[15]		✓	✓
Washington (C+)				✓	12	1	✓		✓	
West Virginia (C-)					18		✓			✓
Wisconsin (C)					16.25	3.5	✓			✓
Wyoming (D-)					12		✓		✓	
District of Columbia (C-)					13		✓	✓		✓
Federal Government (C-)					13		✓	✓	✓	

[10] Pennsylvania state employees receive 1 personal day the 1st calendar year of employment, 2 personal days the 2nd calendar year, and 4 personal days each year thereafter.
[11] Utah state agencies can create sick leave pools for employees with catastrophic illness.
[12] Management employees only are entitled to 3 personal days.
[13] If hired after 1999, Virginia state employees receive 8-10 days of sick leave/year (varies by length of service). If hired prior to 1/1/1999, state employees receive 15 days/year.
[14] If hired after 1999, Virginia state employees receive 4-5 personal days/year (varies by length of service). Employees hired before 1/1/1999 receive no personal leave.
[15] Virginia state employees hired before 1999 can use their sick leave to care for family members. Employees hired after 1999 can only use their personal leave for this purpose.

Chart: State-by-State Summary of Benefits (in rank order)

	State guarantees private sector workers access to paid leave	State provides private sector workers with paid leave to care for a sick family member	State provides private sector workers with paid leave for worker's short-term disability	State requires private employers to allow workers to use paid leave to care for family members	# of paid sick days provided to state employees[1]	# of paid personal days provided to state employees	State employees can use sick/personal leave to care for family members	State employees can access sick leave pool	State employees can take advantage of direct donation program	State employees offered short-term disability insurance
California		✓	✓	✓	12	1	✓		✓	✓
Hawaii			✓	✓	15[2]		✓		✓	✓
New Jersey			✓		15	3	✓		✓	✓
Rhode Island			✓		13	4	✓	✓		✓
New York			✓		10[3]	5	✓		✓	✓
Connecticut				✓	15	3	✓	✓		
Minnesota				✓	13		✓			✓
Washington				✓	12	1	✓		✓	
Maryland					15	6	✓	✓		
Massachusetts					15	3[4]	✓	✓		✓
Alaska					15		✓		✓	✓
Delaware					15		✓	✓	✓	
Illinois					12	3	✓	✓		✓
Montana					12		✓	✓	✓	✓
Oklahoma					15		✓		✓	✓
Wisconsin					16.25	3.5	✓			✓
Alabama					13	1	✓		✓	✓

[1] Only Hawaii, Kentucky, Louisiana, Mississippi, Nebraska, Vermont, Virginia, the District of Columbia, and the federal government tie sick leave to years of service.
[2] 21 days if hired before 7/2/01.
[3] Depending on bargaining units and the date of the employee's hire, New York provides 8, 10 or 13 days of sick leave to state employees.
[4] Massachusetts state police receive 5 days of personal leave as a result of a collective bargaining agreement.

	State guarantees private sector workers access to paid leave	State provides private sector workers with paid leave to care for a sick family member	State provides private sector workers with paid leave for worker's short-term disability	State requires private employers to allow workers to use paid leave to care for family members	# of paid sick days provided to state employees	# of paid personal days provided to state employees	State employees can use sick/personal leave to care for family members	State employees can access sick leave pool	State employees can take advantage of direct donation program	State employees offered short-term disability insurance
Ohio					10	4[5]	✓	✓		✓
Georgia					15		✓		✓[6]	✓
Iowa					18		✓		✓	
New Mexico					12	1	✓		✓	✓
West Virginia					18		✓			✓
District of Columbia					13		✓	✓		✓
Federal Government					13		✓	✓	✓	
Arizona					12		✓		✓	✓
Nebraska					12		✓		✓	✓
Tennessee					12		✓	✓	✓	
Texas					12		✓	✓		✓
Virginia					9[7]	4[8]	✓[9]		✓	✓
Utah					13		✓	✓[10]		✓
Colorado					10		✓		✓	✓
Michigan					13	2	✓			✓
Missouri					15		✓	✓		
New Hampshire					15		✓		✓[11]	

[5] Depending on bargaining unit, Ohio provides 3-5 days of personal leave to state employees.
[6] Georgia provides additional leave on a case-by-case basis.
[7] If hired after 1999, Virginia state employees receive 8-10 days of sick leave/year (varies by length of service). If hired prior to 1/1/1999, state employees receive 15 days/year.
[8] If hired after 1999, Virginia state employees receive 4-5 personal days/year (varies by length of service). Employees hired before 1/1/1999 receive no personal leave.
[9] Virginia state employees hired before 1999 can use their sick leave to care for family members. Employees hired after 1999 can only use their personal leave for this purpose.
[10] Utah state agencies can create sick leave pools for employees with catastrophic illness.
[11] New Hampshire has a supplemental sick leave plan for workers who exhaust leave.

	State guarantees private sector workers access to paid leave	State provides private sector workers with paid leave to care for a sick family member	State provides private sector workers with paid leave for worker's short-term disability	State requires private employers to allow workers to use paid leave to care for family members	# of paid sick days provided to state employees	# of paid personal days provided to state employees	State employees can use sick/personal leave to care for family members	State employees have access to sick Leave pool	State employees can take advantage of direct donation program	State employees offered short-term disability insurance
Nevada					15		✓	✓		
Pennsylvania					13	1[12]	✓		✓	
South Carolina					15		✓	✓		
Florida					13		✓	✓[13]		✓
Oregon					12	2	✓			✓
Vermont					12	✓[14]	✓	✓		
Arkansas					12		✓	✓		
Idaho					12		✓			✓
Indiana					9	3	✓			✓
Kansas					12		✓		✓	
Kentucky					12		✓		✓	
North Carolina					12		✓			✓
North Dakota					12		✓		✓	
Wyoming					12		✓		✓	
Maine					12	2	✓			
South Dakota					14		✓			
Louisiana					12			✓		
Mississippi					12[15]		✓			

[12] Pennsylvania state employees receive 1 personal day the 1st calendar year of employment, 2 personal days the 2nd calendar year, and 4 personal days each year thereafter.
[13] Florida agencies can establish sick leave pools or other methods to provide additional sick leave to employees in need.
[14] Management employees only are entitled to 3 personal days.
[15] Sick leave accrual rate drops after 3 years: after 3 years state employees accrue 10.5 days/year; after 8 years employees accrue 9 days/year; after 15 years employees accrue 7.5 days/year.

Detailed State by State Analysis

ALABAMA (C-)

Private Sector Employees

Alabama has no laws governing access to or use of sick leave for private sector employees.

State Employees

Alabama provides 13 days of sick leave to state employees. Employees who do not live in one of two counties that consider Mardi Gras a holiday are also entitled to one personal day. Sick leave begins to accrue immediately and can be used immediately. State employees can accrue up to 150 days of sick leave. State employees can use their sick leave to care for family members. An employee can receive direct donations of additional paid leave from co-workers who are in an equal or higher pay grade. Alabama provides short-term disability insurance to state employees.

- 13 days of sick leave
- 1 personal day[1]
- Can use for family members
- Direct donation
- Short-term disability for state employees

ALASKA (C)

Private Sector Employees

Alaska has no laws governing access to or use of sick leave for private sector employees.

State Employees

Alaska provides 15 days of sick leave to state employees except those who are in bargaining units that provide paid time off in lieu of paid sick, vacation, or personal days. Employees in bargaining units receive between 24 and 36 days of paid time off depending on their length of service in state government. Sick leave begins to accrue immediately and can be used immediately. There is no limit to how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. An employee can receive direct donations of additional paid leave from co-workers. Alaska provides short-term disability insurance to state employees as an optional benefit.

- 15 days of sick leave
- Can use for family members
- Direct donation
- Short-term disability for state employees

[1] Except in counties where employees receive Mardi Gras as a holiday.

ARIZONA (D+)

Private Sector Employees

Arizona has no laws governing access to or use of sick leave for private sector employees.

State Employees

Arizona provides 12 days of sick leave to state employees. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. An employee can receive direct donations of additional paid leave from co-workers. Arizona provides short-term disability insurance to state employees through a contribution plan.

- 12 days of sick leave
- Can use for family members
- Direct donation
- Short-term disability for state employees

ARKANSAS (D-)

Private Sector Employees

Arkansas has no laws governing access to or use of sick leave for private sector employees.

State Employees

Arizona provides 12 days of sick leave to state employees. Sick leave begins to accrue immediately and can be used immediately. State employees can accrue up to 120 days of sick leave. State employees can use their sick leave to care for family members. A sick leave pool is available for employees who exhaust all of their leave and continue to suffer from a catastrophic illness.

- 12 days of sick leave
- Can use for family members
- Sick leave pool

CALIFORNIA (B+)

Private Sector Employees

Flexible Sick Leave

California requires employers to allow employees to use some of their sick leave to care for a sick child, parent, spouse, or domestic partner. Employees have this flexibility with the number of days of sick leave that they would accrue in six months (at their current level of seniority).

Short-Term Disability

California enacted a short-term disability program in 1946. The program covers nearly all workers in the state and operates through a state-administered disability insurance fund. Employers have the option to provide their own self-insured plans, as long as the plans meet state requirements. The program is funded through employee payroll deductions although employers may elect to pay some or all of the amount that would be paid by the employee. Employees may use this program to replace a portion of their wages if they are unable to work because of a non-work related physical or mental condition, illness, or injury, including pregnancy, childbirth, or a related condition. The maximum benefit period is 52 weeks.

Paid Family Leave

In 2002, California adopted the first paid family leave insurance program in the nation. All employees covered by the state's short-term disability program are qualified to participate. The program provides partial wage replacement for up to six weeks of leave to care for an ill parent, child, spouse, or domestic partner, or to bond with a new baby. The program is funded through employee payroll deductions. Employees cannot receive benefits under the short-term disability program and this program at the same time.

State Employees

California provides 12 days of sick leave and one day of personal leave to state employees. The sick leave begins to accrue immediately and can be used one month after it is earned. Some managers, supervisors, and bargaining units have the option of providing composite paid sick/vacation leave: 22.5 days after one year, 25.5 after ten years, 27 days after 15 years, and 28.5 days after 20 years. The maximum accumulation for those receiving composite paid leave is 80 days. There is no limit on how many sick days an employee can accrue. State employees can use their sick leave to care for family members. An employee can receive direct donations of additional paid leave from co-workers. California provides short-term disability insurance to state employees.

- 12 days of sick leave
- 1 personal day
- Can use for family members
- Direct donation
- Short-term disability for state employees

COLORADO (D)

Private Sector Employees

Colorado has no laws governing access to or use of sick leave for private sector employees.

State Employees

Colorado provides ten days (80 hours) of paid sick leave to state employees. Sick leave begins to accrue immediately and can be used immediately. State employees can accrue up to 45 days of sick leave. State employees can use their sick leave to care for family members. An employee can receive direct donations of additional paid leave from co-workers. Colorado provides short-term disability insurance to state employees.

- 10 days of sick leave
- Can use for family members
- Direct donation
- Short-term disability for state employees

CONNECTICUT (C+)

Private Sector Employees

Flexible Sick Leave

Employees who work for employers with more than 75 employees have the right to use up to two weeks of accumulated sick leave to care for child, spouse, or parent suffering from a serious health condition, or to care for a new baby.

State Employees

Connecticut provides 15 days of sick leave and three days of personal leave to state employees. The sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. Connecticut has a sick leave pool for workers who have exhausted all of their paid leave.

- 15 days of sick leave
- 3 personal days
- Can use for family members
- Sick leave pool

DELAWARE (C)

Private Sector Employees

Delaware has no laws governing access to or use of sick leave for private sector employees.

State Employees

Delaware provides 15 days of sick leave to state employees. The sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. Delaware has a sick leave pool for employees suffering from catastrophic illness. In addition, an employee can receive direct donations of additional paid leave from co-workers.

- 15 days of sick leave
- Can use for family members
- Sick leave pool
- Direct donation

FLORIDA (D)

Private Sector Employees

Florida has no laws governing access to or use of sick leave for private sector employees.

State Employees

Florida provides 13 days of sick leave to state employees. The sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. Individual agencies can create sick leave pools or other programs to provide additional sick leave to employees that exhaust their sick leave benefits. Florida provides short-term disability insurance to management and other selected employees.

- 13 days of sick leave
- Can use for family members
- Agencies can establish sick leave pools or other methods to provide additional sick leave to employees in need.
- Short term disability for some state employees

GEORGIA (C-)

Private Sector Employees

Georgia has no laws governing access to or use of sick leave for private sector employees.

State Employees

Georgia provides 15 days of sick leave to state employees. The sick leave begins to accrue after five days of employment and can be used immediately. State employees can accrue up to 90 days of sick leave. State employees can use their sick leave to care for family members. Additional leave may be requested and is granted on a case-by-case basis. Georgia has a program that makes short-term disability insurance available to employees at their own expense.

- 15 days of sick leave
- Can use for family members
- Additional leave on a case-by-case basis
- Short-term disability for state employees

HAWAII (B)

Private Sector Employees

Flexible Sick Leave

Employers of 100 or more employees must allow employees to use up to ten days of their accrued and available sick leave to care for a child, parent, spouse, or "reciprocal beneficiary" with a serious health condition.

Short-Term Disability

Hawaii enacted a short-term disability program in 1959. The program provides partial wage replacement for employees on leave for non-work related physical illnesses or injuries, including pregnancy and childbirth-related conditions. The program operates by requiring employers to purchase disability insurance, to self-insure, or to guarantee employees this benefit through a collective bargaining agreement. Employers can assume the full cost of the plan or impose some of the cost on employees, with a cap on the employee contribution. The maximum benefit period is 26 weeks.

State Employees

Hawaii provides 15 days of sick leave to state employees hired on July 2, 2001 or later. After ten years of service these employees receive 21 days of sick leave a year. Employees hired before July 2, 2001 receive 21 days of sick leave each year. The sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. An employee can receive direct donations of additional paid leave from co-workers. Hawaii provides short-term disability insurance to state employees.

- 15 days of sick leave - hired 7/2/01 or later
- 21 days of sick leave - hired before 7/2/01
- Can use for family members
- Direct donation
- Short-term disability for state employees

IDAHO (D-)

Private Sector Employees

Idaho has no laws governing access to or use of sick leave for private sector employees.

State Employees

Idaho provides 12 days of sick leave to state employees. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. Idaho offers life insurance plus short and long-term disability insurance at a reduced cost to state employees.

- 12 days of sick leave
- Can use for family members
- Short-term disability for state employees

ILLINOIS (C)

Private Sector Employees

Illinois has no laws governing access to or use of sick leave for private sector employees.

State Employees

Illinois provides 12 days of sick leave and three days of personal leave to state employees. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. Illinois has a sick leave pool for workers who have exhausted all of their paid leave. Short-term disability is funded as part of the state employee retirement system.

- 12 days of sick leave
- 3 personal days
- Can use for family members
- Sick leave pool
- Short-term disability for state employees

INDIANA (D-)

Private Sector Employees

Indiana has no laws governing access to or use of sick leave for private sector employees.

State Employees

Indiana provides nine days of sick leave and three days of personal leave to state employees. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. Indiana provides short-term disability insurance to state employees.

- 9 days of sick leave
- 3 personal days
- Can use for family members
- Short-term disability for state employees

IOWA (C-)

Private Sector Employees

Iowa has no laws governing access to or use of sick leave for private sector employees.

State Employees

Iowa provides 18 days of sick leave to state employees. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. An employee can receive direct donations of additional paid leave from co-workers.

- 18 days of sick leave
- Can use for family members
- Direct donation

KANSAS (D-)

Private Sector Employees

Kansas has no laws governing access to or use of sick leave for private sector employees.

State Employees

Kansas provides 12 days of sick leave to state employees. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. An employee can receive direct donations of additional paid leave from co-workers.

- 12 days of sick leave
- Can use for family members
- Direct donation

KENTUCKY (D-)

Private Sector Employees

Kentucky has no laws governing access to or use of sick leave for private sector employees.

State Employees

Kentucky provides 12 days of sick leave to state employees. After ten years of employment with the state, employees receive 22 days of sick leave a year. After 20 years of employment with the state employees receive 32 days of sick leave a year. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. An employee can receive direct donations of additional paid leave from co-workers.

- 12 days of sick leave
- Can use for family members
- Direct donation

LOUISIANA (F)

Private Sector Employees

Louisiana has no laws governing access to or use of sick leave for private sector employees.

State Employees

Louisiana provides 12 days of sick leave to state employees. After five years of employment with the state, employees receive 18 days of sick leave a year. After ten years of employment with the state, employees receive 21 days of sick leave a year. After 15 years of employment with the state, employees receive 24 days of sick leave a year. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. Agencies can, subject to approval, create their own sick leave pools.

- 12 days of sick leave
- Sick leave pools in some agencies

MAINE (D-)

Private Sector Employees

Maine has no laws governing access to or use of sick leave for private sector employees.

State Employees

Maine provides 12 days of sick leave and two days of personal leave to state employees. Sick leave begins to accrue immediately and can be used immediately. State employees can accrue up to 120 days of sick leave. State employees can use their sick leave to care for family members.

- 12 days of sick leave
- 2 personal days
- Can use for family members

MARYLAND (C)

Private Sector Employees

Maryland has no laws governing access to or use of sick leave for private sector employees.

State Employees

Maryland provides 15 days of sick leave and six days of personal leave to state employees. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. Maryland has a sick leave pool for workers who have exhausted all of their paid leave.

- 15 days of sick leave
- 6 personal days
- Can use for family members
- Sick leave pool

MASSACHUSETTS (C)

Private Sector Employees

Massachusetts has no laws governing access to or use of sick leave for private sector employees.

State Employees

Massachusetts provides 15 days of sick leave and three days of personal leave to state employees. State police receive five days of personal leave as a result of a collective bargaining agreement. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. Massachusetts has a sick leave pool for workers who have exhausted all of their paid leave. Short-term disability insurance is available to state employees who are members of specific unions at the employee's expense.

- 15 days of sick leave
- 3 personal days (5 personal days for state police)
- Can use for family members
- Sick leave pool
- Short-term disability for some state employees

MICHIGAN (D)

Private Sector Employees

Michigan has no laws governing access to or use of sick leave for private sector employees.

State Employees

Michigan provides 13 days of sick leave and two days of personal leave to state employees. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. Michigan provides short-term disability insurance to state employees through a contributory plan.

- 13 days of sick leave
- 2 personal days a year
- Can use for family members
- Short-term disability for state employees

MINNESOTA (C+)

Private Sector Employees

Flexible Sick Leave

Employers with 21 or more employees[2] must allow their employees to use paid sick leave to care for a sick or injured child "for such reasonable periods as the employee's attendance with the child may be necessary."

State Employees

Minnesota provides 13 days of sick leave to state employees. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. Minnesota has a program that makes short-term disability insurance available to employees at their own expense.

- 13 days of sick leave
- Can use for family members
- Short-term disability for state employees

[2] Employers with multiple worksites must have 21 employees in at least one of the worksites in order to be covered.

MISSISSIPPI (F)

Private Sector Employees

Mississippi has no laws governing access to or use of sick leave for private sector employees.

State Employees

Mississippi provides 12 days of sick leave per year to state employees who have worked for the state for three years or less. After three years employees accrue 10.5 days of sick leave a year. After eight years this drops to nine days a year, and after 15 years employees accrue 7.5 days of sick leave a year. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members.

- 12 days of sick leave
- Can use for family members

MISSOURI (D)

Private Sector Employees

Missouri has no laws governing access to or use of sick leave for private sector employees.

State Employees

Missouri provides 15 days of sick leave to state employees. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. Missouri has a sick leave pool for workers who have exhausted all of their paid leave.

- 15 days of sick leave
- Can use for a family member
- Sick leave pool

MONTANA (C)

Private Sector Employees

Montana has no laws governing access to or use of sick leave for private sector employees.

State Employees

Montana provides 12 days of sick leave to state employees. The sick leave begins to accrue immediately and can be used after three months. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. Montana has a sick leave pool for workers who have exhausted their sick leave. Employees can receive direct donations of additional paid leave from co-workers. Short-term disability insurance is available to university system employees.

- 12 days of sick leave
- Can use for family members
- Sick leave pool
- Direct donation
- Short-term disability insurance for some state employees

NEBRASKA (D+)

Private Sector Employees

Nebraska has no laws governing access to or use of sick leave for private sector employees.

State Employees

Nebraska provides 12 days of sick leave to state employees. Employees who have worked for the state for six to 15 years receive 14 days of sick leave a year. After 16 years of service employees accrue 18 days of sick leave a year. The sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. An employee can receive direct donations of additional paid leave from co-workers. Nebraska has a program that makes short-term disability insurance available to employees at their own expense.

- 12 days of sick leave
- Can use for family members
- Direct donation
- Short-term disability for state employees

NEVADA (D)

Private Sector Employees

Nevada has no laws governing access to or use of sick leave for private sector employees.

State Employees

Nevada provides 15 days of sick leave to state employees. The sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. Nevada provides a sick leave pool for employees that have exhausted their sick leave.

- 15 days of sick leave
- Can use for family illness
- Sick leave pool

NEW HAMPSHIRE (D)

Private Sector Employees

New Hampshire has no laws governing access to or use of sick leave for private sector employees.

State Employees

New Hampshire provides 15 days of sick leave to state employees. The sick leave begins to accrue after six months of service, and employees can use their sick leave only after six months of service. State employees can accrue up to 120 days of sick leave. State employees can use their sick leave to care for family members. New Hampshire has a supplemental sick leave plan for workers who exhaust all of their sick leave.

- 15 days of sick leave
- Can use for family members
- Supplemental sick leave plan

NEW JERSEY (B-)

Private Sector Employees

Short-Term Disability

New Jersey enacted a short-term disability program in 1948. The program provides partial wage replacement for most employees on leave because of a non-work related accident or sickness, including pregnancy and childbirth-related disability. Eligible employees are enrolled in the state-administered Temporary Disability Insurance (TDI) plan or are enrolled by their employer in a self-insured plan that is at least equal to the provisions of the state plan. The plan is funded by contributions from both employers and employees. The maximum benefit period is 26 weeks.

State Employees

New Jersey provides 15 days of sick leave and three days of personal leave to state employees. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. An employee can receive direct donations of additional paid leave from co-workers to care for themselves or a sick family member. New Jersey provides short-term disability insurance to state employees.

- 15 days of sick leave
- 3 personal days
- Can use for family members
- Direct donation
- Short-term disability for state employees

NEW MEXICO (C-)

Private Sector Employees

New Mexico has no laws governing access to or use of sick leave for private sector employees.

State Employees

New Mexico provides 12 days of sick leave and one day of personal leave to state employees. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. An employee can receive direct donations of additional paid leave from co-workers. New Mexico provides short-term disability insurance to state employees.

- 12 days of sick leave
- 1 personal day
- Can use for family members
- Direct donation
- Short-term disability for state employees

NEW YORK (B-)

Private Sector Employees

Short-Term Disability

New York enacted its short-term disability program in 1949. The program provides partial wage replacement for employees needing to take leave due to injury or sickness not arising out of work, including pregnancy and childbirth-related disability. The program operates by requiring employers to purchase a disability insurance plan or provide a self-insured plan that meets minimum state requirements. Employees must contribute to the cost of the plan, but the share from the employee is capped and the employer must pay the remaining costs. The maximum benefit period is 26 weeks.

State Employees

New York provides eight, ten, or 13 days of sick leave and five personal days to state employees depending on bargaining units and the date of the employee's hire. Sick leave begins to accrue immediately and can be used immediately. Employees can accrue 200 days or 1,500 hours of sick leave, depending on the employee's bargaining unit. State employees can use their sick leave to care for family members. An employee can receive direct donations of additional paid leave from co-workers. Most state employees rely on their sick leave policies for short-term disability protection.

- 8, 10, or 13 days of sick leave, depending on bargaining unit and date of hire
- 5 personal days
- Can use for family members
- Direct donation
- Short-term disability for some state employees

NORTH CAROLINA (D-)

Private Sector Employees

North Carolina has no laws governing access to or use of sick leave for private sector employees.

State Employees

North Carolina provides 12 days of sick leave per year to state employees. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. North Carolina provides short-term disability insurance to state employees.

- 12 days of sick leave
- Can use for family members
- Short-term disability for state employees

NORTH DAKOTA (D-)

Private Sector Employees

North Dakota has no laws governing access to or use of sick leave for private sector employees.

State Employees

North Dakota provides 12 days of sick leave per year to state employees. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. An employee can receive direct donations of additional paid leave from co-workers.

- 12 days of sick leave
- Can use for family members
- Direct donation

OHIO (C-)

Private Sector Employees

Ohio has no laws governing access to or use of sick leave for private sector employees.

State Employees

Ohio provides ten days of sick leave and three to five days of personal leave, depending on bargaining unit, to state employees. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. Ohio has a sick leave pool for workers who have exhausted all of their paid leave. Short-term disability is made available as part of the state's long-term disability program.

- 10 days of sick leave
- 3-5 personal days depending on bargaining unit
- Can use for family members
- Sick leave pool
- Short-term disability for state employees

OKLAHOMA (C)

Private Sector Employees

Oklahoma has no laws governing access to or use of sick leave for private sector employees.

State Employees

Oklahoma provides 15 days of sick leave per year to state employees. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. An employee can receive direct donations of additional paid leave from co-workers. Short-term disability is provided as an optional benefit.

- 15 days of sick leave
- Can use for family members
- Direct donation
- Short-term disability for state employees

OREGON (D)

Private Sector Employees

Oregon has no laws governing access to or use of sick leave for private sector employees.

State Employees

Oregon provides 12 days of sick leave and two personal days per year to state employees. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. Oregon has a program that makes short-term disability insurance available to employees at their own expense.

- 12 days of sick leave
- 2 personal days
- Can use for family members
- Short-term disability for state employees

PENNSYLVANIA (D)

Private Sector Employees

Pennsylvania has no laws governing access to or use of sick leave for private sector employees.

State Employees

Pennsylvania provides 13 days of sick leave per year to state employees. Employees receive one personal day the first calendar year of employment, 2 personal days the second calendar year, and four personal days each year thereafter. Some corrections officers have paid time off rather than sick, annual, or personal leave. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. An employee can receive direct donations of additional paid leave from co-workers.

- 13 days of sick leave (corrections officers have paid time off)
- 1 personal day first calendar year, 2 days second calendar year, 4 personal days thereafter
- Can use for family members
- Direct donation

RHODE ISLAND (B-)

Private Sector Employees

Short-Term Disability

Rhode Island established its short-term disability program in 1942. The program covers nearly all workers in the state, and operates through a state-administered disability insurance plan. Employees may use this program for partial wage replacement if they are unable to work because of a non-work related physical or mental condition, illness, or injury, including pregnancy or a childbirth-related condition. The program is funded through employee payroll deductions. The maximum benefit period is 30 weeks.

State Employees

Rhode Island provides 104 hours (13 days) of sick leave and four days of personal leave to state employees. Sick leave begins to accrue immediately and can be used immediately. Employees can accrue up to 125 days of sick leave. State employees can use their sick leave to care for family members. Rhode Island has a sick leave pool for workers who have exhausted all of their paid leave. Rhode Island provides short-term disability for state employees.

- 13 days of sick leave (104 hours)
- 4 personal days
- Can use for family members
- Sick leave pool
- Short-term disability for state employees

SOUTH CAROLINA (D)

Private Sector Employees

South Carolina has no laws governing access to or use of sick leave for private sector employees.

State Employees

South Carolina provides 15 days of sick leave to state employees. Sick leave begins to accrue immediately and can be used immediately. Employees can accrue up to 195 days of sick leave. State employees can use their sick leave to care for family members. South Carolina has a sick leave pool for workers who have exhausted all of their paid leave.

- 15 days of sick leave
- Can use for family members
- Sick leave pool

SOUTH DAKOTA (D-)

Private Sector Employees

South Dakota has no laws governing access to or use of sick leave for private sector employees.

State Employees

South Dakota provides 14 days of sick leave to state employees. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members.

- 14 days of sick leave
- Can use for family members

TENNESSEE (D+)

Private Sector Employees

Tennessee has no laws governing access to or use of sick leave for private sector employees.

State Employees

Tennessee provides 12 days of sick leave to state employees. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. Tennessee has a sick leave pool for employees suffering from catastrophic illness. In addition, an employee can receive direct donations of additional paid leave from co-workers if they have used up their allotment from the sick leave pool.

- 12 days of sick leave
- Can use for family members
- Sick leave pool
- Direct donation

TEXAS (D+)

Private Sector Employees

Texas has no laws governing access to or use of sick leave for private sector employees.

State Employees

Texas provides 12 days of sick leave to state employees. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. Texas has a sick leave pool for employees suffering from catastrophic illness. Texas has a program that makes short-term disability insurance available to employees at their own expense.

- 12 days of sick leave
- Can use for family members
- Sick leave pool
- Short-term disability for state employees

UTAH (D+)

Private Sector Employees

Utah has no laws governing access to or use of sick leave for private sector employees.

State Employees

Utah provides 13 days of sick leave to state employees. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. Utah agencies can create sick leave pools for employees suffering from catastrophic illness. Utah has a program that makes short-term disability insurance available to employees at their own expense.

- 13 days of sick leave
- Can use for family members
- Sick leave pools at agency discretion
- Short-term disability for state employees

VERMONT (D)

Private Sector Employees

Vermont has no laws governing access to or use of sick leave for private sector employees.

State Employees

New employees are advanced six days of sick leave. After that employees receive 12 days of sick leave for the first five years. After ten years of service employees receive 15 days of sick leave a year. After 15 years of service employees receive 18 days of sick leave a year. And, after 20 years employees receive 21 days of sick leave a year. Management employees are also entitled to three days of personal leave; after five years management employees are entitled to four days of personal leave, and after ten years they receive five days of personal leave. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees can use their sick leave to care for family members. Vermont has a sick leave pool for employees suffering from catastrophic illness.

- 12 days of sick leave
- 3 days of personal leave for management employees
- Can use for family members
- Sick leave pool

VIRGINIA (D+)

Private Sector Employees

Virginia has no laws governing access to or use of sick leave for private sector employees.

State Employees

Virginia provides 15 days of sick leave to employees hired prior to 1999; employees hired after 1999 receive eight to ten days of sick leave and four to five days of personal leave based on length of service. Sick leave begins to accrue immediately and can be used immediately. There is no limit on how many sick leave days an employee can accrue. State employees hired before 1999 can use their sick leave for family members. Employees hired after 1999 can only use their personal leave to care for family members. An employee can receive direct donations of additional paid leave from co-workers. Short-term disability is provided to employees hired after January 1, 1999 and to others who opt into the program.

- 8-10 days of sick leave – hired 1/1/1999 or later (varies by length of service)
- 15 days of sick leave – hired before 1/1/1999
- 4-5 personal days – hired after 1/1/1999 (those hired before 1999 receive no personal leave)
- Can use sick leave for family members if hired before 1/1/1999; can use only personal leave for family members if hired after 1999
- Direct donation
- Short-term disability for state employees hired after 1/1/1999 and for others who opt into the program

Disclaimer

While text, citations, and data for this report were, to the best of the authors' knowledge, current as ***Get Well Soon: Americans Can't Afford to Be Sick*** was prepared, there may be subsequent developments, including recent legislative actions, which could alter the information provided herein. This report does not constitute legal advice; individuals and organizations considering legal action should consult with their own counsel before deciding on a course of action.

National Partnership for Women & Families

News Release

News Release
June 15, 2004

Contact: Myra Clark Siegel, 202/986-2600
Lisa Lederer, 202/371-1999

States, Federal Government Failing to Provide Minimal Paid Sick Days to American Workers

No State Merits Grade of "A" in New Report Card

Washington, D.C. – Not a single state is doing all it should to guarantee paid sick leave to employees, according to the most comprehensive analysis ever of the laws and regulations governing paid sick leave in the United States. States and the federal government are doing a poor job of ensuring that workers can use paid sick days to care for ailing children and other relatives, and of governing private sector policies. As a result, millions of American workers must choose between their paycheck and recovery each time they get the flu, break a bone, or need to care for an ailing child, spouse or parent.

Those are among the findings of ***Get Well Soon: Americans Can't Afford to be Sick***, a new report from the National Partnership for Women & Families that was released at a news conference today at which lawmakers introduced The Healthy Families Act. Co-sponsored by U.S. Senator Edward M. Kennedy (D-MA) and Representative Rosa L. DeLauro (D-CT), The Healthy Families Act would guarantee seven paid sick days per year for full-time employees, and a pro-rata amount for part-time employees. It would cover public and private sector employers with at least 15 employees. "No one who works for a living should have to choose between the job they need and the family they love," Senator Kennedy said. "That is why I am introducing legislation to guarantee that workers have access to paid sick days, to help millions of American families address the work-family balance."

Get Well Soon reports that 47 percent of private sector workers and 59 million total workers in the U.S. have no paid sick leave at all, according to the Institute for Women's Policy Research. Some 86 million workers do not have paid sick leave that can be used to care for sick children. "The findings paint a picture of need and neglect," said National Partnership President-Elect Debra L. Ness. "The failure to provide paid sick days to workers causes profound harm to families, and unnecessary costs to businesses, which pay to recruit and train new workers when providing paid sick leave to employees already in place would cost considerably less. It's past time to remedy this shameful situation. The failure to provide paid sick leave exacts a terrible toll from families, businesses and our nation."

Get Well Soon finds that California is far ahead of other states in giving workers family leave benefits; it receives a grade of "B+" in the study. Hawaii receives a "B," and New Jersey, New York and Rhode Island each receive a "B-." Mississippi and Louisiana rank worst in the nation, receiving grades of "F." Arkansas, Idaho, Indiana, Kansas, Kentucky, Maine, North Carolina, North Dakota, South Dakota and Wyoming receive grades of "D-."

Add One

The federal government receives a grade of "C-." It gives federal workers 13 paid sick days a year – relatively generous compared to the private sector, but no better than what many states offer their own employees. And the federal government lags behind several states in that it does not require private employers to provide any paid sick leave.

Another new study, to be released later this week by The Project on Global Working Families at Harvard University, finds that the U.S. lags far behind the rest of the world in giving workers paid sick days. One hundred thirty-nine nations provide paid leave for short or long term illnesses, and 117 of those nations guarantee their workers a week or more of paid sick leave per year. However, no federal law in the U.S. guarantees a single day of paid sick leave to workers. The federal Family & Medical Leave Act (FMLA) provides only unpaid leave for serious illnesses to the approximately 60 percent of the workforce that it covers.

In the U.S., need is particularly acute among low-wage and female workers. Three in four low-wage workers in the U.S. (76 percent) have no paid sick leave. The Urban Institute recently reported that 41 percent of working parents have no paid leave of any kind – no paid sick leave, no paid vacation and no paid personal days off. Last year, the Kaiser Family Foundation reported that half of working mothers (49 percent) said they do not get paid when they stay home to care for a sick child.

"Paid sick leave is the next frontier in the effort to make our nation's workplaces more family-friendly," Ness added. "It's time to put our family values to work. We commend the sponsors of The Healthy Families Act for addressing a critical need. Americans will be watching closely to see if the lawmakers they elected support this essential measure."

"It is hard to believe that in this country almost 50 percent of workers have to choose between risking their jobs or going to the doctor when they are sick," Representative DeLauro said. "With this legislation we move one step closer to guaranteeing that all workers can obtain a minimum amount of paid sick days so they can deal with their medical needs or those of their family members."

Get Well Soon authors awarded points to each state based on the programs made available to private and public sector employees. As most employees work in the private sector, the point system favors laws that provide protection and benefits to private sector employees. For private sector workers, researchers examined: job protected paid sick days; family leave benefits available to care for seriously ill family members, infants or newly placed adoptive and foster children; short-term disability programs; and requirements that employers let workers use paid sick days to care for family members. For public sector workers, researchers examined paid sick days, paid personal days, sick leave pools and other measures.

# # # #

The National Partnership for Women & Families is a non-profit, non-partisan advocacy group dedicated to promoting fairness in the workplace, quality health care and policies that help Americans balance the demands of work and family. A National Partnership staff attorney wrote the federal FMLA, and the organization led the decade-long fight to pass it. The FMLA was enacted nearly eleven years ago over protests from businesses. More than 40 million Americans have benefited to date. Get Well Soon *is available at www.nationalpartnership.org*

Statement of Rep. Ed Towns (NY-10)
before the Government Reform Committee

Committee on Government Reform

"The Nation's Flu Shot Shortage:
Where Are We Today and How Prepared Are We For Tomorrow?"

Wednesday, November 16, 2004
1:00pm

Thank you, Mr. Chairman. I am very pleased that the Committee is holding this hearing. As the details of the flu vaccine problem continue to come in, I cannot help but think that the shortage could and should have been prevented. The fact that a bacterial infection in the United Kingdom has led to this much chaos in America is astounding to me. We should have been better prepared.

Our constituents, especially our seniors and high-risk citizens, have been understandably traumatized by the flu vaccine shortage. Hopefully, we will use this past year's dilemma productively in order to ensure that it never happens again. My colleagues and I must remember that above all else, America's health should be our number one priority.

I understand that when Chiron's license was suspended, the FDA conducted its own investigation of the Fluvirin facility at Chiron. The FDA subsequently announced that the U.S. would not receive any of the 45-50 million doses of Chiron's Fluvirin inventory. This single decision effectively hand-cuffed the people of the United States, as there was no back-up plan to provide flu vaccine. Are we working on one now? I certainly hope so. Again, we should have been better prepared.

I applaud the efforts of Aventis Pasteur and its quest to deliver 8 million doses by early December. I look forward to that relief and to the additional 2.6 million doses promised by early January. I have been informed that Aventis and the Centers for Disease Control plan to redirect any vaccines that had not been distributed by the fifth of October. I'm curious to hear about the progress on that endeavor.

There seems to have been a great deal of confusion, missed opportunity for help and a faulty set of protocols that led to the shortage. If the communication between the FDA, Britain's MHRA and Chiron was ineffective, then tell us what steps need to be taken. In my opinion, the protocols regarding early notification and troubleshooting were contributing factors to the epidemic. As I'm sure everyone in this room knows, Congress could not operate effectively without punctual and open communication. It is evident to me that neither were present between the parties involved in the shortage. Had certain people and agencies

been notified of the pending problem ahead of time, this hearing would not have been necessary. Open communication is *essential* -- I cannot stress this enough. However, I am mindful and appreciative of Chiron's efforts to remedy the situation and I hope new measures are in the works.

As we speak, 16 vaccine manufacturers and officials from the U.S. and other countries are meeting in Geneva at the World Health Organization to address the flu epidemic. In that a flu pandemic occurs every 27 years, with the last one happening in 1968, I hope that progress is made and I look forward to the results of the summit.

In the meantime, I hope that our panelists have viewed the past year's problems with an educational and concerned eye, and I thank them for appearing today. As I said at the beginning of my remarks, our constituents and America as a whole cannot go through this again. The health of our citizens is paramount, and we should everything in our legislative power to safeguard it.

Thank you, Mr. Chairman. I yield back the balance of my time.

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Statement of Congresswoman Carolyn B. Maloney
Hearing: "The Nation's Flu Shot Shortage: Where Are We Today and How Prepared Are We for Tomorrow"
November 17, 2004
Room 2154, Rayburn House Office Building

Thank you Chairman Davis and Ranking Member Waxman for holding this important hearing today.

I would also like to thank our distinguished witnesses. With your insight, I hope to learn how we could have avoided this situation and how we can prepare for the future.

Like everyone here, I am very concerned by what has transpired over the past 3 months. Influenza is a serious risk to many Americans. Three times as many Americans die from influenza as the number who are victims of homicide. About 2/3 as many Americans die of the flu each year as die from all types of accidents. It is clear, the flu is very serious, and we must be very serious about how we deal with the problem.

It is for this reason that I am concerned by the sequence of events. It is my understanding that John Taylor, FDA's associate commissioner for regulatory affairs, told the Wall Street Journal that in 2003, FDA's Liverpool's inspection showed "systemic quality-control issues" at the Chiron facility. Unfortunately, despite these known problems, FDA never returned to the plant to verify that things had been rectified and that the vaccine would meet minimum safety standards. Instead, FDA chose to rely on Chiron's assurances that deficiencies had been corrected. What's worse, even after Chiron announced on August 27 that it had identified contamination in a portion of its flu vaccine, FDA did not schedule an inspection. It makes one wonder: if FDA had responded quickly to the August 27th announcement, could we have avoided the severity of the problem? Moreover, had FDA alerted Aventis Pasteur of the problem, could FDA have redirected their vaccine to high-risk individuals? After all, by the time the announcement was made, Aventis had already shipped almost 60% of the vaccine, but they had not been shipped before Aug. 27. Again, a quick response could have helped more people.

I would like to take this opportunity to publicly acknowledge and thank New York City Mayor Michael Bloomberg for taking the initiative to partner with Illinois and New Mexico officials to buy 200,000 does of flu vaccine from European suppliers. While this is not enough to cover all residents, it's an adequate amount to inoculate the City's high-risk residents. Once

FDA approves the doses, NYC will have 575,000 doses of vaccine. I, along with 8 of my colleagues from New York, sent a bipartisan letter to Commissioner Crawford asking FDA to expedite the review process for these doses. I hope to hear about the progress of the evaluation today.

Again, the problem is real. According to NYC health department Commissioner, Thomas Frieden, 1,000 and 2,000 people die a year in the city from flu and pneumonia. Two flu outbreaks in nursing homes in the city have led to four deaths and 13 hospitalizations in the past few weeks. While I am grateful to our mayor, I believe that the Federal Government must bear the responsibility of providing safe and available vaccine to all those in need.

Thank you.

Statement of Congressman Elijah E. Cummings
House Government Reform
Full Committee Hearing
"The Nation's Flu Shot Shortage: Where We Are Today and How Prepared Are We For Tomorrow"
November 17, 2004 at 1:00 p.m.
2154 Rayburn House Office Building

Thank you, Mr. Chairman.

I want to thank you for holding this second hearing to discuss the current influenza vaccine shortage.

On August 26, 2004, the Chiron Corporation, the fifth largest vaccine producer in the world and one of the three flu vaccine manufacturers licensed by the Food and Drug Administration (FDA), informed that it would delay shipment of any Fluvirin doses because some of the vaccine lots did not meet product sterility specifications. On October 15, the FDA, after learning of Chiron's license suspension by the British Medicines and Healthcare Products Regulatory Agency (MHRA) on October 5, 2004, and after conducting its own investigation of the company's Liverpool manufacturing facility, informed that Chiron's flu vaccine would not be accepted for use in the United States this year. It was expected to supply the United States with 45-50 million doses.

During the emergency hearing held on October 8, 2004, this Committee heard testimony on the contributing factors that lead to the current shortage. Based on the testimony presented and the Committee's investigation, we concluded that the FDA had "responded adequately" and followed "routine protocol" regarding Chiron's early August announcement. However, it is nonetheless disturbing that the FDA had been made aware of the strong possibility of a flu vaccine shortage in late August when Chiron announced that several lots were infected with bacteria, yet did not take the necessary actions to secure additional vaccinations nor to suspend vaccinations to the general non-risk public. Upon further investigation by the Committee, it was discovered that the FDA knew of serious problems at Chiron's facility as early as June 2003, but did not exercise its oversight authority properly to correct them.

Mr. Chairman, as you are well aware, Congress has appropriated several billion dollars in our effort to enhance public health preparedness. Yet, despite our efforts during last year's flu season, the U.S. was ill-prepared for the early and severe outbreak of influenza that managed to claim the lives of 129 youth (all under the age of 18), as reported by the Centers for Disease Control (CDC) on February 5, 2004. In fact, every year over 36,000 people

die and over 200,000 more are hospitalized from complications arising from the flu. Many billions of manpower hours are lost due to complications arising from the flu. As such, proactivity in addressing our nation's vaccine needs is critical.

As you know Mr. Chairman, it was not until October 15th, that we were made aware of the shortage despite the FDA's knowledge in August 2004 of a possible shortage. Now, it is evident that the FDA knew of the problems at Chiron since June 2003 -- discovered during its routine two-year inspection. Had the FDA reacted more authoritatively during these critical time periods, we could have reacted differently to ensure our most vulnerable populations were protected. Additionally, had the FDA acted even earlier, an additional 50 million shots could have been procured from Aventis Pasteur , in early September, the other leading U.S. flu vaccine supplier. This news makes me ask the questions: what must be done to ensure that our nation is prepared for adequate production of the flu vaccine and who should be responsible for making sure it's done – no excuses.

Our nation must be prepared to safeguard our citizens to prevent an outbreak of communicable diseases. If we are to expect excellence of our

public health preparedness system, then we must provide the proper means by which this can be accomplished.

I hope that in your testimonies today you will address the following questions: in the future, how should the FDA better respond to the knowledge of a possible shortage, what can we do to ensure that there be better communication between the FDA and the British government regulatory agencies. Currently, in light of the new evidence of the FDA's culpability in the flu shortage crisis, I would like to know what corrective action measures the FDA is taking to ensure this never happens again?

With that said, I look forward to hearing from our witnesses and once more thank you, Mr. Chairman, for holding this hearing.

I yield back the balance of my time.

Statement of Dennis Kucinich
U.S. House of Representatives
Committee on Government Reform

Hearing: "The Nation's Flu Shot Shortage: Where are We Today and How Prepared are we for Tomorrow?"
November 17, 2004

Thank you for the opportunity to speak, Chairman Davis about this critical public health issue that has affected the entire US. While investigations are still underway as to what exactly went wrong that caused the Flu vaccine shortage this year, it is already clear the FDA ignored early warning signs and is circling the wagons in a defensive posture.

In June of 2003, the FDA inspected Chiron's manufacturing facility in the UK and found 20 major problems, including recurring problems. The FDA then had the option to enforce violations as recommended by their own inspectors but opted to let Chiron handle it alone, preferring to wait until the next required inspection to check for corrections to the violations... in 2005. The FDA could have sent a warning letter to document the violations, which would have reserved the right to initiate enforcement actions later and would have alerted the public. And Chiron might have taken the violations more seriously.

In fact, Chiron sent a letter to the FDA after their inspection requesting a meeting to discuss ways to handle the problems that were found. The FDA refused, which is what they say they usually do with these kinds of requests under normal circumstances. But the circumstances are not normal when the facility has a history of violations and manufactures half of the US Flu vaccine supply and 20% of the British Flu vaccine supply.

In August 2004, the FDA missed another clear warning signal when Chiron announced contamination of 5 million doses of Flu vaccine. But in order to alleviate fears of an impending shortage, Chiron testified to Congress that it would still be able to provide the US with its full vaccine order. The FDA did not travel to the UK to inspect the facility for verification, again relying on Chiron's word that the problem was being addressed.

To get the FDA to conduct a facility inspection, it took the announcement in October of this year, that Chiron's British manufacturing license was revoked.

The cumulative impact of the FDA's failure remains to be seen as the Flu season approaches. At a minimum, earlier knowledge of the threat of a shortage clearly would have allowed the CDC to recommend a delayed distribution of vaccine stock from Aventis, the other major flu vaccine manufacturer. The result would have been more vaccines going to higher risk Americans instead of the lower risk people who were vaccinated before the CDC redirected supplies.

Unfortunately it appears as though the FDA has no interest in learning from its mistakes. In the weeks after the shortage announcement in October, they refused to release documents surrounding their 2003 inspection in which major violations were found. Now that the election is over, the documents have been released and for the first time we are starting to get a picture of what happened. FDA failures appear to be part of a larger culture of deference to industry at the expense of public health. Still, public statements made by the agency declare that, if they had it to do all over again, they wouldn't change a thing.

I look forward to finding out why that is the case.

Opening Statement
Congresswoman Diane E. Watson
Government Reform Committee

Hearing entitled "The Nation's Flu Shot Shortage: Where Are We Today and How Prepared Are We For Tomorrow"
11/17/04

Thank you Mr. Chairman. I want to commend you for calling this hearing before the end of the year. The Government Reform Committee has an important public service to perform in regards to the flu vaccine shortage. With only a few vaccine manufacturers producing flu vaccines each year, Congress must consider what can be done to strengthen the market and increase domestic production capabilities.

United States based Chiron Corporation is the fifth-largest vaccines producer in the world. Chiron produces Fluvirin™ influenza vaccine, which is one of only two injectable flu vaccines approved by the United States Food and Drug Administration. Aventis, the French vaccine company, manufacturers flu vaccine in Pennsylvania for the U.S. market.

Although one of the two FDA approved flu vaccine manufactures is American, Chiron does not have a production facility located on U.S. controlled soil. The Chiron production facility is in the British city of Liverpool.

Biological preparedness is considered crucial in the current world climate. Our government has no other control over a natural phenomenon that will threaten citizens every year. Flu pandemic has the ability to cause death in catastrophic proportions.

Mr. Chairman, I am concerned about our national position in a very sensitive health care area. Prior to the Chiron shutdown announcement, The British Medicines and Healthcare products Regulatory Agency purchased an additional 2 million doses of flu vaccine from other manufacturers in case more problems with the Chiron facility arose. The United

States was not afforded any advance warning. In addition to the lack precautionary action, the physical location of the Chiron manufacturing plant has severely limited the options of the FDA. In the future, should a flu pandemic occur, it can be theorized that the UK could restrict Chiron's vaccine supply, again resulting in the loss of half of the U.S. flu vaccine supply.

To address the flu vaccine issue Congress must work to reinvigorate the domestic manufacture of vaccines. As a start, Representative Emanuel has introduced H.R. 3758 that mirrors Senate bill 2038,

introduced by Senators Bayh, Craig, Landrieu, and Durbin. The bill would mandate a flu vaccine awareness campaign and educational efforts. This bill would also create a vaccine manufacturing facilities investment tax credit. Furthermore, it would require CDC to purchase as many doses of flu vaccine as the Director of CDC deems is necessary. The legislation would mandate that the Director of CDC establish a protocol to respond to a flu pandemic, and would compel a vaccine manufacturer that intends to leave the vaccine market to notify HHS of its intent to withdraw.

Mr. Chairman, I look forward to today's testimony, and the positive solutions that our witness can provide. I am interested to hear their assessment of the Emanuel bill. We need a much better system in place to accommodate vaccine shortage or increased demand situations. I urge Congress to rapidly move forward in the decision making process. I again commend our Committee for an immediate response to a serious public concern. I yield back the balance of my time.

Congressman Michael C. Burgess, M.D.
Government Reform Committee
"The Nation's Flu Shot Shortage: Where are We Today and How Prepared are We for Tomorrow?"
Wednesday, November 17, 2004

It is unsettling that with prior experience dealing with an influenza vaccine shortage last flu season that we would be in a similar, if not more severe situation this Fall and Winter. I am pleased that Chairman Davis and the Government Reform Committee has taken such an aggressive approach to investigating this health crisis. I believe that this Committee should continue this investigation to satisfy many of the questions raised by this situation. In a broader sense though, I believe that we need to look at the underlying causes of this crisis.

This situation gives us an impetus to make important changes in how manufacturers produce influenza vaccine and how we can secure a dedicated supply of the vaccine. Both regulatory and legal reforms would create an environment more suited to stabilizing the supply of vaccines in this country.

At a Government Reform Committee hearing on October 8, 2004, Dr. Anthony Fauci, Director of the National Institutes for Allergy and Infectious Diseases, talked about how streamlining production of the influenza vaccine could remove many of the quality control issues that have been on display in the latest Chiron incident. Replacing the egg-growth step in vaccine production and replacing it with cell culture method will optimize production in many ways. For one, with a cell culture technique, annual flu production could be re-started within a season if a problem does arise. By utilizing a technique that is more flexible than the current egg-growth method, problems with vaccine shortage could be largely mitigated. While this growth technique is still in development and in the early stages of clinical trials, I am hopeful that the National Institutes of Health will continue to support research such as this.

Just as current production methods can constrain the availability of vaccine, other economic and legal issues place additional pressures on vaccine manufacturers, putting patients at even greater risk. Coupled with low profitability, high production failure, and an antagonistic liability system, many manufacturers have opted out of producing influenza vaccine. Currently there are only TWO manufacturers producing injectable flu vaccine for the U.S. market in 2004. As recently as the 2001-2002 flu season, the United States had three manufacturers producing injectable vaccine, but one has since dropped out of the market.

Because the government is such a large purchaser of vaccine, government contracts can act as a price setting mechanism for vaccine throughout the sector. While this may be unavoidable in the sense that vaccine delivery via public health outlets is an accepted and

traditional model of vaccination in the United States, adding a legal system that can be extremely adversarial at times only serves to compress participation in the market.

In October 2004, the U.S. Congress added flu vaccine to the list of vaccines covered under the National Vaccine Injury Compensation Program (VICP). While this program has proven to be successful in limiting liability costs for a wide range of vaccine producers over the years and fairly compensating families who have suffered an injury or death attributed to a vaccine, it just shows how deleterious the liability system was in relation to flu vaccine manufacturers prior to October 2004 as some manufacturers dropped out of the market. While the addition of influenza to the VICP list should deter many unnecessary lawsuits, VICP does not cover certain additives to vaccines, exposing manufacturers to additional liability. Because influenza vaccine manufacturers produce hundreds of millions of doses in a given season, their legal exposure increases exponentially, creating a situation not faced by many other vaccine manufacturers.

Like treating a patient, it is necessary to treat the symptoms of an illness, but to cure one you have to address the root causes of the disease. I am pleased that Chairman Davis has undertaken an investigation to deal with the symptoms of this situation and look forward to working with him to find a cure. Thank you.

Infectious Diseases Society of America

Recommendations for Strengthening U.S. Preparedness and Response to Pandemic Influenza

November 15, 2004

The Infectious Diseases Society of America (IDSA) recently submitted detailed recommendations to the Department of Health and Human Services (HHS) on the agency's Draft Pandemic Influenza Preparedness and Response Plan.

While IDSA applauds HHS's efforts on a thoughtful and scientifically based plan, the Society has proposed a number of recommendations that, if incorporated, could help to strengthen the U.S. and global response to an influenza pandemic.

Among other things, IDSA has called for a regular, perhaps annual, timetable to update the plan so that it can remain current and evolve with science and policy. IDSA believes it is important for the plan to emphasize international collaboration and outline a role for the United States to help the world prepare for and respond to an influenza pandemic.

IDSA offered HHS recommendations in the following areas and urges Congress to consider these recommendations as it deliberates influenza preparedness and response efforts this fall:

- **Coordination and stakeholder buy-in:** IDSA calls for a pre-established strategy to facilitate rapid communication between HHS and other federal agencies, state and local public health officials, medical societies, physicians, and other health professionals. Specifically, IDSA recommends that the National Vaccine Program Office (NVPO) should have ultimate responsibility for coordinating efforts within HHS and with other federal agencies. As such, NVPO would oversee domestic and international influenza activities, including surveillance and supply of vaccines and antivirals.
- **Coordination and accountability of the research agenda:** IDSA recommends forming an advisory committee to coordinate the various influenza research efforts being undertaken by government agencies, independent researchers, and industry. A progress report should be compiled and published on a regular basis.
- **Consistency of recommendations and implementation:** Given the confusion that has resulted during this year's flu shot shortage, IDSA calls for clear, national guidelines to identify--in advance of a pandemic--priority groups for vaccine and antiviral use, as well as containment methods and strategies to decrease the transmission of disease.
- **Interpandemic influenza:** There is much to be learned about how best to respond to a pandemic influenza outbreak, during the annual influenza season. IDSA urges the federal government to use this time and the lessons learned during these annual outbreaks wisely. Specifically, IDSA recommends strengthening vaccine and antiviral distribution networks; investing in research to advance what we know about influenza and how best to respond; developing prevention, control and treatment strategies; identifying resource needs; and building infrastructure and capacity.
- **Vaccine supply:** Because the influenza virus changes from year to year, a reliable stockpile of flu vaccine cannot be built beforehand. However, IDSA recommends that small seed stocks of candidate vaccine strains be developed and tested. Because the pneumococcal vaccine can prevent

certain complications of influenza, the Society recommends that HHS consider stockpiling this vaccine. IDSA also urges the development of specific and realistic plans to rapidly create a vaccine in sufficient quantity, as well as a system to track the distribution of vaccine and antivirals.

- **Antiviral supply:** IDSA recommends stockpiling antiviral drugs that can be used to treat influenza and stop the spread of infection. A specific strategy should be developed to distribute antiviral drugs to states, local health departments, and other points of care.
- **Legislation to spur development of vaccines and antivirals:** IDSA advocates legislation to spur the research, development, and licensing of new vaccines and antivirals. Specific strategies worth exploring include market incentives, risk reduction, liability protections, compensation for injury, intellectual property rights, tax credits for research, and a guaranteed federal purchase plan.
- **Funding:** IDSA believes that the Administration's request of $100 million for pandemic influenza activities in fiscal years 2004-2005 seriously underestimates the amount of funds realistically needed to effectively respond to the next pandemic. An investment in infrastructure and capacity to effectively respond to influenza will yield benefits every year, whether or not a pandemic occurs. In addition, IDSA believes that, in the event of a flu pandemic or other serious infectious disease outbreak, the Executive Branch should be able to trigger an emergency funding mechanism so that federal officials may respond quickly.

IDSA submitted specific comments on the draft plan to HHS on October 26. The comments are available on the Society's website at www.idsociety.org.

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IDSA is an organization of physicians, scientists, and other health care professionals dedicated to promoting human health through excellence in infectious diseases research, education, prevention, and patient care. The Society, which has nearly 8,000 members, was founded in 1963 and is headquartered in Alexandria, Va. For more information, visit www.idsociety.org.

Written Testimony of

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Submitted to

UNITED STATES HOUSE OF REPRESENTATIVES
COMMITTEE ON GOVERNMENT REFORM

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"The Nation's Flu Shot Shortage: Where Are We Today, and How Prepared Are We for Tomorrow?"

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Mr. Chairman and members of the Committee, thank you for the opportunity to submit testimony on the nation's current shortage of flu vaccine and its significance to the American public health system. As a non-profit, non-partisan organization dedicated to saving lives by protecting the health of every community and working to make disease prevention a national priority, Trust for America's Health (TFAH) believes that vaccines have proven to be one of the most effective interventions in the history of public health. That is why the production halt of approximately half of this season's influenza vaccine is a troubling development for our nation. It exemplifies the lack of overall preparedness in the U.S., not just with respect to the flu, but also on a wide range of potential public health crises. A strong and rapid-response vaccine defense can effectively protect Americans from either bioterrorism (anthrax) or Mother Nature (pandemic flu). The bad news is that today the U.S. public health defenses are not adequately prepared for either threat.

The flu strikes an estimated 10 to 20 percent of the U.S. population and is responsible for approximately 36,000 deaths each year. Yet this nation does not have a unified and effective flu management strategy. Nor have policy makers made the necessary investments to protect Americans from unanticipated contingencies -- ranging from the emergence of a possible new flu strain that could cause a pandemic to problems with the vaccine supply. This latest complication sends a message loud and clear -- now is the time to fix the hit and miss approach to the flu and to implement a national vaccine policy that protects the American public from a wide range of preventable illnesses.

2004 FLU CRISIS: A FIRE DRILL FOR A BIO-TERROR EVENT?

Over the past few weeks, we have seen Americans frustrated as they line up for limited flu shots. We have watched public health officials scramble for supplies and doctors pleading for guidance on how to prioritize a limited vaccine supply. The apparent good news is that the U.S. is not facing a severe influenza outbreak this year -- preliminary signs point to a mild flu season that has just begun to impact a handful of states. Unfortunately, however, the long lines, limited oversight of vaccine distribution, and poor communications among public health professionals and the public have provided yet another wake-up call about the importance of planning and preparing for major health emergencies.

Health experts are particularly worried about an inevitable pandemic influenza outbreak that could result in millions of deaths and hospitalizations. If the avian bird flu mutated into a highly transmissible virus, with a 35 percent infection rate and only one percent mortality impact, computer projections estimate that 252,659 Americans would die in the first wave of an outbreak. The ongoing threat of bioterrorism agents, including highly communicable diseases like smallpox, remains viable. To be prepared for whatever health threat that might develop, Americans deserve a sustained, strategic commitment at the federal, state and local levels to strengthen the nation's public health defenses.

What It Will Take to Achieve Adequate Public Health Preparedness:

- Leadership, Planning, and Coordination. *An established chain-of-command and well-defined roles and responsibilities for seamless operations between different medical and scientific functions during crisis situations.* The 2002 Bioterrorism Security Act requires all states to develop preparedness plans for a public health emergency, whether terrorist-induced or natural. Overall, the General Accountability Office (GAO) found in its 2004 report that few states met the CDC's critical benchmarks for development of a statewide response plan and development of a regional response plan.

  Despite calls for pandemic flu preparations from leading health organizations such as Association of State and Territorial Health Officials (ASTHO), the Council of State and Territorial Epidemiologists (CSTE) and the World Health Organization (WHO), a wide gap remains with respect to planning for an influenza pandemic. TFAH reported last year that only 13 states had draft pandemic influenza plans in place. After ten years in the making, the Department of Human Health and Services (DHHS) finally released its draft pandemic influenza plan this past summer. CDC now encourages states to include pandemic planning as part of their "all hazards" approach to emergency preparedness but does not actually track, review or evaluate these plans.

  The flu vaccine shortage provided another glimpse into the limited preparedness and authorities that states have in health emergencies. Only 16 states issued emergency orders or rules for vaccine distribution. Such orders allow more effective crisis management and provide direction to health care providers, the public and other interested parties. For instance, an emergency declaration protects physicians from hostile patients who were low risk but demanding shots; increases the public health community's ability to inform the public on risk avoidance strategies and actions; and provides clearer mandates for redistribution of vaccines and efforts to stop price gouging.

- Expert and Comprehensive Workforce. *Highly-trained and fully-staffed experts of scientists and other public health professionals.* A series of reports in 2003 by the Institute of Medicine (IOM), CSTE and GAO found that public health agencies are severely understaffed in the areas of public health nursing, environmental health specialists, health educators, epidemiologists, and administrative personnel. The GAO noted that "staffing shortages are a major concern" and that the demands on new emergency planning activities often divert time from the "usual activities" of public health workforce staffers. The personnel shortage also has affected pandemic influenza planning and responsiveness. As a stopgap measure, DHHS recently launched its Cities Readiness Initiative aimed at preparing postal workers to respond in public health crises. Unfortunately, this effort diverted funds from states that were attempting to remedy workforce shortages. To address the need for a sustained and competent team at federal, state and local health agencies, Congress should pass the Public Health Preparedness Workforce Act of 2004.

- Modernized Technology. *State-of-the-art laboratory equipment, information collection, and health tracking systems.* As a result of preparedness funding, the majority of states have significantly improved their laboratory capacity for testing influenza. But most states still need additional facilities for a major biological event and almost all continue to suffer from inadequate staffing.

  Further, CDC and states have limited ability to track actual flu cases, deaths and even locations of medical supplies. This limited disease surveillance capacity was apparent during last year's flu crisis as concerns about children's death rates skyrocketed among parents and the general public. During the actual flu season, CDC was unable to determine if the influenza strain was more virulent for children since the agency did not have the ability to track childhood deaths. Even with increased preparedness funding, few resources have gone into creating a nationwide health-tracking network, leaving most states unlinked to CDC and continuing to use paper-based reporting systems. There is one promising development however. The National Association of County and City Health Officials (NACCHO) has recently initiated a vaccine tracking system so that all doses can be inventoried and monitored throughout the country, allowing health authorities to access up-to-date information on critical supplies.

- Pre-Planned, Rapid Emergency Response Capabilities and Precautions: *Tested planning and safety precautions to mitigate potential harm to communities and public health professionals and first responders.* In the event of a pandemic, states would need to be able to rapidly distribute medical supplies and equipment to hard-hit or at-risk areas. As the current flu vaccine shortage has revealed, many states did not have clear oversight, experience or staffing to handle distribution. The Department of Homeland Security and CDC's color-coded designations for states preparedness to distribute vaccines and medicines only highlights this gap. In fact, TFAH believes that only three states have "green" status for being fully prepared to receive the Strategic National Stockpile -- the emergency cache of medical materials that will be delivered by federal authorities in the event of a health disaster. Further, DHHS claims that a majority of states can inoculate their population within ten days, though health experts do not believe any state actually has such capacity in place.

- Immediate, Streamlined Communications Capabilities: *Coordinated, integrated communication among all aspects of the public health system and with the public.* With the bioterrorism funding, almost 90 percent of the U.S. population resides in areas with health departments directly linked to CDC through the Health Alert Network. The next stage is to ensure rapid communications with key health partners, such as laboratories, hospitals and pharmacies. In May 2004, CDC found that states still had considerable room for improvement in emergency outreach: only eight percent of states were able to contact their partners within 20 minutes; 55 percent could contact most partners and 37 percent were able to contact only some partners in that same time period.

Nothing is more sacred than protecting the health and safety of all Americans. In this regard, Congress should continue its commitment to bolstering the nation's public health defenses. Given the wide range of health threats facing the United States, starting with the current flu vaccine crisis, strategic investments now will have a huge pay off in terms of the health and well-being of all Americans.

VACCINES: A LIFE-SAVING RETURN ON INVESTMENT

Less than a hundred years ago, tens of thousands of infants, children and adults died or were severely disabled by debilitating diseases like smallpox, polio, mumps or diphtheria. Today, incidences of these diseases have been reduced significantly -- in some cases, even eradicated -- thanks to vaccines. In the wake of September 11, 2001 and the subsequent anthrax attacks, vaccines also have become critical to ensuring the nation's biosecurity

In addition to saving lives and improving the quality of life, immunization generates significant economic benefits. According to an extensive cost-benefit analysis by the Centers for Disease Control and Prevention (CDC), every dollar spent on immunization saves $6.30 in direct medical costs, with an aggregate savings of $10.5 billion. When including indirect costs to society -- a measurement of losses due to missed work, death and disability as well as direct medical costs -- the CDC notes that every dollar spent on immunization saves $18.40, producing societal aggregate savings of $42 billion. This represents a significant return on investment, yet marketplace disincentives and other challenges have seriously eroded the public health protections provided by vaccines.

In recent years, U.S. vaccine policy as a public health defense has fallen short, leaving millions at risk and costing thousands of lives. A myriad of problems have converged, threatening the future viability of the nation's vaccine capacity, coverage and commitment.

Consider the scope of complex issues related to vaccine policy:

- Vaccine Safety. The public has become increasingly concerned about the safety of vaccines. Recently, military personnel and medical professionals have refused smallpox and anthrax vaccines due to health concerns. In 1999, the public health service belatedly recognized that Thimersol-laden vaccines were causing children to exceed "safe" levels of mercury. Suggestions about autism links to MMR vaccines in early childhood have long lingered, despite a lack of evidence. This growing distrust can weaken public support for one of the most effective disease prevention tools. Since its creation in 1986, the National Vaccine Injury Compensation Program (VICP) has made many awards following injuries deemed to have been associated with CDC-recommended vaccinations. Majority Leader, Bill Frist, MD, believes this program should be reviewed along with other vaccine safety issues and has introduced legislation to do so.

- Ineffective Vaccines. Due to excessively long and complex production processes, scientists must make educated guesses about what viral strains might circulate months before the start of each influenza season. For the last flu season, the wrong strains were targeted, severely reducing the vaccine's efficacy. Should a pandemic or an unexpectedly virulent strain emerge, this country's antiquated manufacturing system could not rapidly respond. In response, the government is working to make possible cell-based cultures as opposed to the current egg-based cultures with respect to the flu vaccine. This change should make the process more stable and dependable, but much work remains.

- Vaccine Shortages. According to a report of the National Vaccine Advisory Committee, an "unprecedented and unanticipated shortage of recommended vaccines occurred in the United States beginning in 2001, resulting in significant and extended shortages of routinely administered vaccines against eight of eleven vaccine-preventable childhood infectious diseases." In many cases, immunization was deferred, posing an increased risk of otherwise preventable infectious disease. Studies found a number of reasons for shortages, including: companies leaving the vaccine market; manufacturing and production problems; and insufficient stockpiles and distribution systems. For instance, despite shortages in the traditional flu vaccine in 2003, a recent private vaccine innovation -- an aerosolized influenza vaccine -- struggled, in part, because of the lack of an adequate national vaccine program. The current Chiron debacle only underscores the nation's vulnerability.

- Marketplace Concerns. In 1976, 37 U.S. companies manufactured vaccines; in 2002, there were only ten. Why? Reasons given are mostly economic. Vaccine production can take decades of research and development and, according to industry estimates, costs about $800 million per licensed vaccine. Concerns about potential liability sometimes keep manufactures out of the vaccine business, especially after the huge compensations claims that followed the swine flu immunization program in the mid-1970s. For other companies, there is insufficient market size in the United States to warrant the effort. For example, Malaria, tuberculosis, and HIV kill five million and sicken 300 million worldwide annually. Yet, aside from HIV, manufacturers have little incentive to develop vaccines because U.S. incidence and incentives are low.

- Producer Concentration. In the U.S. and global vaccine industries, there is the increasing possibility that more and more important vaccines will be produced by a single firm, often in a single production facility. Are sole-source suppliers a weak link in the U.S. vaccine supply chain? For terrorists intent on negating the effect of a vaccine on a weaponized biological agent, disabling the manufacturing facility first may be a very attractive target. Accordingly, several questions arise, including, is a federal policy for vaccine supply assurance necessary, and what form should it take? Are the recommendations of the Institute of Medicine's Committee on Emerging Infections for a publicly owned "standby production capacity" of critical vaccines feasible or cost-effective? These issues are beginning to capture Congressional attention. At a recent

House Government Reform hearing, Chairman Tom Davis noted, "that in event of a public health emergency, either terrorist or natural, U.S. may not have access to vital vaccines."

- Access. Successful development and production of a safe and effective vaccine does not ensure that everyone who needs a vaccine gets it. People have to (1) know about it and believe it will benefit them; (2) live near a health care provider willing to administer it; and (3) be able to afford the cost of vaccination and follow-up care, if necessary. Sadly, only 76 percent of U.S. children under three years old had completed the recommended series of vaccinations in 2000 despite the Healthy People 2000 and 2010 objectives of 90 percent. Recommended adult immunization rates are even farther from Department of Health and Human Service (HHS) goals. In addition, there are regional and economic disparities in access to immunization services. Reasons given for these problems include insufficient coordination of varying eligibility rules among private insurers and government vaccine programs; incomplete documentation of immunizations achieved; and inadequate financing at both the federal and state level.

- Competing Jurisdictions. There is no central authority for vaccine policy within the federal government. The Food and Drug Administration (FDA) is responsible for the regulation of vaccines and other biologics. Other agencies that have jurisdiction for vaccine policy include the Department of Health and Human Services (e.g., the National Institutes of Health, the Centers for Disease Control and Prevention's (CDC) National Vaccine Program and the National Immunization Program and its Advisory Committee on Immunization Practice, and the Health Resources and Services Administration's (HRSA) Vaccine Injury Compensation Program, which is jointly administered by the U.S. Court of Federal Claims and the U.S. Department of Justice), and the Departments of Defense, Veterans Affairs, and Homeland Security.

Simply stated, the United States needs to revamp its vaccine policies. The time has come In order to ensure that Americans are protected from naturally occurring diseases or acts of bioterror a non-partisan commission should be convened to build consensus around a 21st century national vaccine policy and generate the political will and resources to implement it. This will mean bridging long-standing differences about the goals of vaccine policy among manufacturers, the legal profession and the public health community. That said, the recent convergence of significant issues around vaccine modernization in general and its impact on bioterror preparedness, has resulted in the forging of new alliances to address vaccine modernization that transcend political and ideological barriers.

The current flu debacle was predicted and predictable. It does not, however, have to be repeated.

Mr. Chairman and Members of the Committee, thank you again for the opportunity to express TFAH's views on this important public health issue.

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Nov. 16, 2004
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- To the House Committee on Government Reform -
- Hearing, Nov. 17, 2004, 1:00 p.m. -
- Rayburn House Office Building, Room 2154 -

- ``The Nation's Flu Shot Shortage: Where Are We Today -
- And How Prepared Are We for Tomorrow?" -

- Testimony for the Record -
- From Lyndon LaRouche Political Action Committee -

- TAKE ALL MEASURES TO DEAL WITH THE IMMEDIATE THREATS -
- OF FLU AND OTHER DISEASES; REVERSE THE -
- POLICIES THAT ARE CREATING PUBLIC-HEALTH CRISES -

To Committee Chairman, Rep. Tom Davis; Rep. Henry Waxman, and Committee Members:

In recent weeks, members of this Committee have rightly undertaken a necessary line of investigation into the current U.S. flu shot supply shortage, namely: How did it come about, that the U.S. 2004-05 flu vaccine was to come from only two suppliers, including one company reliant on an off-shore facility, with a known history of risk? Throwing a spotlight on this question is important. But in terms of government oversight, we want with this testimony to bring attention to the broadest context within which to judge government responsibility:

First, what is the full scope and nature of the disease threat faced today by this nation and internationally--going beyond even pandemic influenza?

Second, from that vantage point, what are the public-health and other actions called for in the immediate situation, and what must be done to reverse the policies that created the crises in the first place?

The particulars of the various dramatic episodes in recent years, including the anthrax attack (2001), SARS (2003), Mad Cow Disease in North America, etc., illustrate the point that it is the takedown of public-health infrastructure, along with globalization practices in agriculture and throughout the economy, that are themselves causing increased likelihood of harm.

Forewarning was given decades ago by American economist and Democratic Party leader Lyndon LaRouche, who in 1973, commissioned a task force on the prospects for a ``biological holocaust,'' if policies of de-industrialization and free trade were to prevail, and to create ``points of congruity and interaction of economic and biological processes,'' leading to the spread of disease. In July 1985, the task force published the {EIR} Special Report ``Economic Breakdown and the Threat of Global Pandemics.''

Unfortunately, LaRouche's warnings have been borne out. We are now seeing dramatic, deadly proof of how new and re-emerging diseases are associated with practices of outsourcing, lack of sanitation and pest eradication, monoculture in agriculture, and all the other hallmarks of so-called ``competitive global sourcing and markets.''

Moreover, bad as this free-trade era was when it ``worked,'' it is now simply breaking down.

Lyndon LaRouche on July 30 of this year addressed the issue of the public-health crisis, and the general collapse process in the economy, at a Boston press conference following the end of the Democratic Party Convention; there he announced the formation of the political action committee Lyndon LaRouche PAC, to fight for emergency measures to restore a functioning {physical economy.}

During September and thereafter, LaRouche PAC put out 800,000 copies of a mass pamphlet on that very point, {It's the Physical Economy, Stupid!}

During October, LaRouche PAC put out 1.5 million mass leaflets on the flu vaccine debacle, to jolt the public and lawmakers alike into facing what responsible government should be doing, instead of writing off the sick and poor.

LaRouche stressed on July 30, that people block on what's right in front of them. ``You see a country that is being destroyed while people are talking about prosperity and improvement of conditions of life. In fact, when you look at the physical reality, per county, across the entirety of the United States; look at the standard of living; the capital investment; the infrastructure; per county, across the United States. You see a nation which has been physically destroyed, in which those who consider themselves wealthy are in the upper 20% of family-income brackets, and more and more concentrated in a few areas.'' There are bubbles of housing real-estate values and the like, while manufacturing, health care, and necessities of life are collapsing.

``...The physical reality of the condition of the United States--has to be brought to the consciousness of people, who see this, but they look at it as if they didn't see it. They say, `But we see, the report is that

the economy is getting better.' Look at the reality: The economy is getting worse."

That's what lies behind the government malfeasance in failing to see to flu shots, and failing to provide for medical care.

- Threat of Flu Pandemic, Other Diseases -

For years, epidemiologists and livestock and other experts have sounded alarms about growing disease threats. Three recent sources make the necessary points about the scale of danger today, beginning with influenza.

{Pandemic Flu}. On Oct. 28, Dmitri Lvov, director of the Ivanovsky Virology Institute and Academician of the Russian Academy of Medical Sciences, held a press conference (source: RIA-Novosti News Agency), warning of the threat of avian flu becoming transmissable human to human. ``Up to 1 billion people could die around the whole world in six months. We are half a step away from a worldwide pandemic catastrophe."

The World Health Organization, the Pan American Health Organization, the International Vaccine Institute, based in Seoul, South Korea, and many other agencies, are likewise warning of flu pandemic.

On Sept. 25, 2004, a report given to the Pan American Health Organization conference warned of a potential ``new influenza strain" saying that the ``sudden and marked change in Influenza virus A [in Asia] should be considered one of the greatest public-health concerns" in the Americas. The report said, ``Recent episodes of animal strains causing disease in humans support experts' views that a new pandemic is inevitable.... Epidemiological studies project that another pandemic is most likely to result in ... 280,000 to 650,000 deaths in less than two years--in industrialized countries alone."

{New and Re-Emerging Diseases}. Apart from influenza, there are threats from other new and re-emerging infectious diseases. A September 2004 report by the Government Accountability Office (GAO), ``Emerging Infectious Diseases," reviewed how well state and Federal surveillance systems are set up to monitor disease incidence. Provided at the request of Sen. Norm Coleman, Chairman of the Permanent Subcommittee on Investigations of the Senate Committee on Governmental Affairs, the study took place over the past year, and the report includes a world map showing many of the ``Selected Emerging Infectious Diseases, 1996-2004."

On the flu, the GAO report stressed: ``The Centers for Disease Control and Prevention (CDC) estimates that if an influenza pandemic were to occur in the United States, it could cause an estimated 314,000 to 734,000

hospitalizations and 89,000 to 207,000 deaths, with associated costs ranging from $71 to $167 billion." (From the CDC, {Fiscal Year 2005, Justification of Estimates for Appropriations Committees}, p. 172.)

On disease threats generally, the GAO report states, ``More than 36 newly emerging infectious diseases were identified between 1973 and 2003, and new emerging infectious diseases continue to be identified."

{Microbial Threats}. The U.S. crude death rate from infectious diseases, declining for 80 years, is now on the rise! The National Institutes of Medicine, which surveys rates of infectious diseases every 10 years, released its 400-page report in 2003--{Microbial Threats to Health; Emergence, Detection and Response}--and stressed at the outset that in the United States, the crude death per 100,000 persons from infectious diseases has increased from 1980 to 1999, from under 40 deaths to over 50, and this is before the death toll from HIV/AIDS is added in. With that included, {the U.S. death rate from infectious diseases has risen from 40 per 100,000 in 1980, to over 60 by the turn of the century}!

Why? The Institutes of Medicine faults the head-in-the-sand policies of the past 20 years, in which the public and lawmakers discontinued base-line public-health policies, perhaps under the delusion that disease threats had somehow come to an end! ``As a result of this apparent reprieve from infectious diseases, the United States Government moved research funding away from infectious disease toward the `new dimensions' of public health--noncommunicable disorders such as heart disease and lung cancer. The government closed `virtually every tropical and infectious disease outpost run by the U.S. military and Public Health Service' [quote from a 1989 study by Garrett]. Infectious disease surveillance and control activities were deemphasized. Research, development, and production of new antibiotics and vaccines declined. The potentially devastating impact of infectious diseases was either relegated to the memory of previous generations or left to the imagination of science fiction enthusiasts...."

All kinds of infectious diseases are on the rise--not simply recent and exotic varieties such as West Nile Fever, or Lyme disease. Two cases in point: whooping cough and food-borne illnesses.

* Whooping cough, or pertussis. The seventh-ranked killer infection globally, this is making a comeback in the United States, due to lack of vaccination, poverty, immigration, and general neglect. In 2003, some 13 children died due to pertussis, which can also cause pneumonia and inflammation of the brain. In 2004, the CDC reported that North Dakota has had one of the largest

outbreaks, with 693 cases in 2004, up from just six in 2003.

* Hepatitis A. In October-November 2003, the largest-ever U.S. outbreak from a single source took place near Pittsburgh, in Beaver Valley, Pennsylvania. At least 650 got sick; 100 were hospitalized; three died, two men (aged 38 and 46), and a 51-year-old woman. The source was contaminated scallions, imported from a cheap-labor farm operation in Mexico. Another incident may occur at any time. During the winter months, up to 70% of the fresh fruits and vegetables consumed in the U.S. are imported; the average annual rate is 25-35% and rising. Harmful pathogens are more than three times as likely from low-infrastructure sources in Mexico, Guatemala, the Philippines and elsewhere, including salmonella, E. coli, and shigella.

{Zoonotics and Botanicals}. Beyond basic sanitation and pathogens, risks of disease are increasing, simply because of the common patterns of plant-life and livestock-raising under globalized agriculture, and lack of public-health infrastructure under borderless ``free trade" generally.

The threat comes from the fact that the last 40 years have been characterized by ever-increasing monoculture in crops and livestock, increasing reliance on a few varietals of plants and animals, and dangerous animal husbandry practices. Therefore, vulnerability and extent of damage are maximized, in the case of any mutation, outbreak, species-jump, etc.

One recent case of plant disease, and magnified harm from monoculture, is the arrival this fall of soybean rust, a fungus, in the United States for the first time (confirmed Nov. 10 by the U.S. Department of Agriculture). The blight, of the species {Phakopsora pachyrhizi}, was identified in Louisiana. It can cut yields significantly. The same fungus--entrenched in Asia--arrived in South America in 2001, and has spread since, reaching Argentina in 2003.

The salient point about this pest, is that food cartel-imposed policies have led to a situation of such concentration that only three countries of the Americas--the United States, Brazil, and Argentina--together account for 188 million metric tons, which is over 80% of all world annual soy production (229 million metric tons), and those three account for over 90% of all soybean exports. There is no redundancy and no reserves.

The cartel companies (ADM, Cargill, Monsanto, Smithfield et al.) imposing extreme concentrations of food processing, factory-farm-production monoculture, and trading, have been extensively documented by Prof. William

Heffernan, of the University of Missouri.

Animal sources of diseases are equally serious, both for risk of direct transmission, and as ``mixing bowls'' for mutations of pathogens that can then become human-to-human transmissable. The GAO September report summarized, ``According to CDC, nearly 70% of emerging infectious disease episodes during the past 10 years have been zoonotic diseases, which are diseases transmitted from animals to humans. The West Nile virus, which was first diagnosed in the United States in 1999, is an example of a zoonotic disease. The West Nile virus can cause encephalitis, or inflammation of the brain.... Other zoonotic diseases include SARS, avian influenza, human monkeypox, and variant Creutzfeldt-Jakob diseases (vCJD), which scientists believe is linked to eating beef from cattle infected with bovine spongiform encephalopathy (BSE) and is often called mad cow disease....''

Look at the record of the period of origins and spread of BSE in Britain, under Prime Minister Margaret Thatcher, the quintessential free-marketeer government (1980-90).

After the 1970s, studies by the U.S. Department of Agriculture and others were finding risks of ``transmissable dementias'' between species, the strong recommendation was made in September 1979, that hygiene standards be tightened for animal feeds in Britain, where a large outbreak of sheep scrapie was underway (TSE, transmissible spongiform encephalopathy). The British Royal Commission on Environmental Pollution wanted tight licensing for processing animal proteins--especially sheep parts--back into the feed and food chain, especially the chain destined for cows.

Thatcher and her Agriculture Minister Lord Peter Walker refused, on grounds that this violated the privatization principle of ``self-regulation'' of farm and health industries; they loosened rules on cycling animal wastes back into feed; and on exporting animals. By 1986, BSE was identified; by 1996, some 162,000 cases of BSE cows were officially reported in the U.K., and the epidemic had been exported.

- Government Responsibility -

These kinds of ideologies must be stopped cold, and public-health principles re-established as the basis for government action. The current U.S. flu shot debacle underscores that very point.

What needs to be done in the short term is straightforward, generally falling into two categories: vaccines and medical treatment contingencies.

{Vaccines}. Both for the 2005-06 ``normal'' flu season, and for the threat of a killer flu pandemic, the

United States government must take domestic actions, and collaborate internationally, to see to a ramping-up of vaccine production capacity, and to back the best science and production of a potentially useful avian flu vaccine. Currently, two companies are tasked to make some 2.4 million shots of an experimental vaccine. {It is of the utmost importance to evaluate and vastly expand that program.}

The Nov. 11-12 unprecedented ``Flu Summit'' of 50 government leaders and 16 vaccine manufacturers in Switzerland, has created a an institutional forum through which a crash program of vaccine production can take place, if the United States and collaborating nations act on this.

The ``Flu Protection Act,'' sponsored by Senators Evan Bayh and Larry Craig, and many others, has been introduced into Congress, and includes the initiatives essential to ensuring the needed volumes of vaccine. The measures contained in this bill have been endorsed by the American Public Health Association, the American Lung Association, and many other organizations.

{Medical treatment contingencies.} Also in the short term, Federal intervention is required to aid states and localities to provide contingency plans for hospital emergency rooms and beds, anti-viral medicines, staff and so on, to handle any surge of patients caused by the fact that in this 2004-05 season, the United States lacks half the expected flu shots.

The need for contingency logistics has in fact been heightened, because Federal authorities did not take timely action immediately after Oct. 6--the day of the announcement of the delicensing of the Chiron plant in Liverpool--to collect and re-allocate scarce flu shots. Thus closed a window of opportunity for at least mitigating the chaos, and that means that harm will now be inevitable.

The takedown of the U.S. hospital system, Veterans Administration hospitals, and public-health agencies has been so drastic over the past three decades of the ``managed care'' ideological era, that even a mild flu season, with plentiful vaccine, has seen hospitals overwhelmed. The Homeland Security fund infusions of 2002-04 have in no way reversed the net decline of the U.S. health system.

On Oct. 18, the American College of Emergency Physicians, an organization of 22,000 doctors, meeting in San Francisco issued a plea for Federal action and resources to be able to handle the coming wave of patients.

- Return to `Hill-Burton' Principle -

The principle to guide both short-term contingency medical arrangements, and the restoration of the U.S. health system, is the traditional American health-care policy known historically as the ``Hill-Burton'' principle. This refers to the 1946 bipartisan law, ``The Hospital Survey and Construction Act.'' This simple, nine-page law mandated that every county in the nation must provide hospital facilities on a ratio of licensed beds per 1,000 residents, based on modern medical standards of treatment. During the years from the late '40s through the mid-1970s, this policy led to the successful provision of hospital beds in nearly all 3,069 counties, at a ratio of 5.5 beds per 1,000 in rural areas, and 4.5 per 1,000 in urban areas (where transportation was easier).

During the 1950s and '60s, the same ``Hill-Burton spirit'' governed the aggressive efforts to defeat poliomyelitis and other diseases, as a matter of principle.

Then came the dismantling of this system, and the thinking behind it, with the passge in 1973 of the first HMO furtherance act, the subsequent deregulation of health care, and the concept of ``managing'' care, instead of combatting disease.

Today's flu vaccine fiasco in the United States underscores the point that generally, the {economic system itself} is now breaking down; along with it, the ideologies that rationalized the economic takedown all along, are disgraced. We face the opportunity and the necessity to return to the principles and tasks of restoring the physical economy--in particular, health care.

This is a bipartisan duty of the highest level. Senator Harold Burton was a Republican from Ohio; Senator Lister Hill, a Democrat from Alabama. Both were advocates of industry, agriculture, and public-serving infrastructure, as well as health care, in particular.

Your leadership on this Committee, on the particular matter of flu vaccine, can provide a needed impetus across the board to bring about the collaborative steps necessary to restore the health-care system, and the economy itself.

On Oct. 6, Lyndon LaRouche, asked about the significance of the 50-million-flu-shot cancellation, during an international webcast in Washington, D.C., said, ``To put the human race at risk in this way, was a mistake! We have to adopt a policy of correcting that mistake, by reversing the policies which led to that mistake.... Do whatever it takes.''

STATEMENT OF THE
AMERICAN COLLEGE OF PHYSICIANS
TO THE
HOUSE COMMITTEE ON GOVERNMENT REFORM
For the Record of the Hearing
"The Nation's Flu Shortage: Where Are We Today and How
Prepared Are We for Tomorrow?"
November 17, 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.

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Public Health Legal Preparedness Materials

Material Related to the Influenza Vaccine Shortage

The following legal materials may be of use to persons researching the 2004 - 2005 influenza vaccine shortage in the United States. Researchers should also visit the CDC influenza website and the websites of relevant individual jurisdictions. Materials are listed in alphabetical order by jurisdiction.

- Federal. SB 2968. Short Title: Emergency Flu Response Act of 2004. A bill amending the Public Health Service Act to address the flu vaccine shortage. (Introduced 10/8/2004)
  (.PDF file)
  (Posted: 10/22/2004 11:00 AM)

- National. Collection of legal orders and materials concerning the 2004-2005 influenza vaccine shortage, posted by the National Association of County and City Health Officials.
  (Web link)
  (Posted: 10/13/2004 10:00 AM)

- National. Department of Defense. Interim Policy Guidance for the Use of Influenza Vaccine for 2004-2005 Flu Season. A memorandum prepared by William Winkenwerder, Jr., MD, Assistant Secretary of Defense for Health Affairs, concerning interim policy guidance for the administration of available vaccine.
  (PDF file)
  (Posted: 10/19/2004 10:00 AM)

- National. The Association of State and Territorial Health Officials (ASTHO). Resources for the Influenza Season 2004-2005. This ASTHO site contains various information on the limited flu vaccine supply and recommendations, as well as the efforts by states to effectively target vaccine and implement federal guidelines for the 2004-2005 influenza season.
  (Web link)
  (Posted: 10/14/2004 1:00 PM)

- California. A Health Order issued by Alameda County Health Officer ordering that all providers of the influenza vaccine limit the administration of the vaccine to those in the high risk category. (National Association of City and County Health Officials).
  (PDF file)
  (Posted: 10/21/2004 11:00 AM)

- California. Alameda County Health Officer provides rational for Emergency Health Order. County Health Officer provides justification for declaring an Emergency Health Order for flu vaccine shortage. (National Association of City and County Health Officials).
  (PDF file)
  (Posted: 10/21/2004 1:00 PM)

- California. A Health Order issued by the City of Berkeley, Department of Health and Human Services of Public Health ordering health care professionals to comply with orders to limit the

administration of vaccine to those in the high risk category. (National Association of City and County Health Officials).
(PDF file)
(Posted: 10/21/2004 12:00 AM)

- California. Mayor of San Francisco Proclaims Local Emergency. An order directing health care providers limit vaccination to individuals that are in the high risk category. (National Association of City and County Health Officials).
(Word file)
(Posted: 10/21/2004 12:00 AM)

- California. Los Angeles County. A copy of an influenza vaccine memorandum advising supervisors of the Los Angeles Department of Health Services of the department's plan for responding the flu vaccine shortage.
(PDF file)
(Posted: 10/20/2004 3:00 PM)

- California. Los Angeles County. Sample copies of letters prepared by the County of Los Angeles Department of Health Services requesting local health care providers and skilled nursing facilities to limit their distribution of the influenza vaccine to those persons listed in the high risk priority group.
(Word file); (Word file)
(Posted: 10/20/2004 3:00 PM)

- California. Order to Control Influenza Vaccination. Order by the California State Health Officer ordering all health care providers in California to limit influenza vaccination to persons in high-risk groups. Signed by the Health Officer on October 8, 2004. Authority cited: Cal. Health & Safety Code, Sections 100180 and 120140.
(PDF file)
(Posted: 10/13/2004 10:00 AM)

- Connecticut. Emergency Executive Order. An Executive Order issued by the Governor of Connecticut requiring certain agencies administering trivalent inactivated influenza vaccines to give priority to individuals who are members of high risk or targeted populations.
(Word file)
(Posted: 10/25/2004 4:00 PM)

- Connecticut. Title 42 Chap743h. A chapter from the General Statutes of Connecticut dealing with price gouging during an emergency.
(Web link)
(Posted: 10/21/2004 10:00 AM)

- Connecticut. A memorandum published by the State of Connecticut Department of Public Health providing information and guidelines addressing the shortage of the flu vaccine. (Courtesy of the National Association of County and City Health Officials).
(PDF file)
(Posted: 10/13/2004 3:00 PM)

- D.C. DC Flu Vaccine Emergency Rule. A copy of the flu vaccine Emergency Rule issued by Gregg A. Pane, MD, Acting Director of the DC Department of Health, mandating that available influenza vaccine held by District health care providers be used for priority groups only, and imposes penalties for noncompliance. Authority cited: s. 3(a) of the Preventive Health Services Amendments Act of 1985 ("Act"), effective February 21, 1986, D.C. Law 6-83, D.C. Official Code § 7-131(a) and Mayor's Order 98-141, dated August 20, 1998, hereby gives notice of the adoption, on an emergency basis, of an amendment to Chapter 2 of Title 22 of the District of Columbia Municipal Regulations (DCMR) (Public Health and Medicine) (August 1986).
(Web link)
(Posted: 10/18/2004 3:00 PM)

- Delaware. An Order to Control Influenza Vaccination signed by Delaware Health and Social Services Secretary Vincent P. Meconi ordering that the influenza vaccine be administered

only to those individuals in the high risk category. Authority Cited: Title 16, Section 122 of Delaware Code, Health and Safety
(Web link)
(Posted: 10/27/2004 3:30 PM)

- Florida. Press Release. Statement from Florida Department of Health Secretary of John O. Agwunobi, MD, MBA, MPH encouraging influenza vaccination prioritization for high risk individuals, and authorizing the distribution of flu vaccine between doctors, hospitals, and pharmacies during the 2004-2005 flu season.
(Word file)
(Posted: 10/13/2004 4:00 PM)

- Florida. An Emergency Rule issued by the Florida Department of Health authorizing the administration of surplus influenza vaccine by health care entities to be administered to specified priority high risk groups. Authority cited: s. 499.012(1)(a)2.b. F.S.
(Word file).
(Posted: 10/13/2004 4:00 PM)

- Hawaii. DOH Priority Guidelines provides priority guidelines on the administration of influenza vaccine to high risk populations.
(PDF file).
(Posted: 11/9/2004 10:00 AM)

- Iowa. Public Health Bulletin. Issued October 11, 2004, by the Iowa Department prioritizing the administration of the influenza vaccine. Authority cited: s.135.11(3).
(PDF file).
(Posted: 10/20/2004 11:00 AM)

- Kansas. Guidance on Priority Groups for Inactivated Influenza Vaccination. Guidelines provided by the Kansas Department of Health and Environment that specifically define high risk groups and assists vaccine providers in the responsible use of flu.
(PDF file).
(Posted: 10/20/2004 4:00 PM)

- Maine. Updated Guidance on Influenza. A memo from the Maine Department of Health, State Health Officer Dora Anne Mills provides additional updated guidance to various Emergency Departments, Hospital Associations, and Local Health Departments on the administration of the extremely limited influenza vaccine.
(Web link)
(Posted: 10/14/2004 11:00 AM)

- Maryland. Governor's Call for Prioritization of Flu Vaccine. A press release issued from the Office of the Governor and the Department of Health and Mental Hygiene announcing that Maryland will adopt recommendations issued by CDC for the prioritization of the flu vaccine.
(Web link)
(Posted: 10/13/2004 3:00 PM)

- Massachusetts. Boston. Revised Emergency Influenza Vaccine Order. A revised emergency order issued by the Boston Public Health Commissioner requiring the distribution of the flu vaccine be limited to those individuals in the high risk categories, and imposes penalties for noncompliance. Authority cited: M.G.L. c. 111, s.5A.
(PDF file)
(Posted: 10/26/2004 12:00 AM)

- Massachusetts. Boston. Emergency Flu Regulation. Emergency flu regulation enacted by the board of the Boston Public Health Commission governing the distribution and priorization of flu vaccine in the city of Boston.
(PDF file)
(Posted: 10/26/2004 12:00 AM)

- Massachusetts. Massachusetts Flu Vaccine Initiatives. Massachusetts Public Health

Commissioner Christine Ferguson issues a public health order to limit flu vaccination to people in the high risk groups.
(Web link)
(Posted: 10/14/2004 11:00 AM)

- Michigan. Michigan Public Health Order. A copy of a health order issued by Janet Olszewski, Director, Michigan Department of Community Health to limiting the administration of the influenza vaccine to those priority populations outlined by the CDC, and imposes penalties for noncompliance.
(PDF file)
(Posted: 10/18/2004 1:35 PM)

- Missouri. An Executive Order signed by the Governor of Missouri Bob Holden ordering all health care providers to limit influenza vaccinations to individuals in the high risk category.
(PDF file)
(Posted: 10/27/2004 3:35 PM)

- Nebraska. Health Alert Network. Guidelines developed by the Nebraska Health and Human Services for specifically defining high risk groups for the influenza vaccination
(PDF file)
(Posted: 10/13/2004 3:00 PM)

- New Jersey. S1997. A bill authorizing the Commissioner of Health and Senior Services to reallocate flu vaccine to high-risk persons, and imposes penalties for non compliance. Approved by Governor 10/27/2004; became P.L.2004, c.153.
(Web link)
(Posted: 11/1/2004 10:00 AM)

- New Jersey. An Order issued by the New Jersey Commissioner of Health and Senior Services authorizing the reallocation of influenza vaccine to certain priority groups, and imposing penalties for non compliance.
(PDF file)
(Posted: 11/5/2004 2:00 AM)

- New Mexico. New Mexico Public Health Order. Order issued by the Secretary of the New Mexico Department of Health limiting the administration of influenza vaccine to those individuals who are most at risk for serious illness or death due to influenza, and imposes penalties for noncompliance. (Courtesy of the National Association of County and City Health Officials).
(PDF file)
(Posted: 10/13/2004 3:00 PM)

- New York. Dutchess County Emergency Health Order. A press release from the Dutchess County Commissioner of Health, mandating that only individuals who meet the CDC priority population guidelines be administered the flu vaccine, and announcing the revised flu vaccination clinics. (The National Association of County and City Health Officials).
(Web link)
(Posted: 10/18/2004 3:00 PM)

- North Carolina. N.C.A.C. 41A.0201. An administrative rule that states that the Centers for Disease Control and Prevention's recommendation regarding which priority groups should receive influenza vaccination is an enforceable rule referenced in the NC Administrative Code.
(PDF file)
(Posted: 10/22/2004 9:30 AM)

- Oklahoma. Executive Proclamation issued by Oklahoma Governor urging health care providers to reserve the flu vaccine for those individuals who are in high risk categories.
(Web link)
(Posted: 10/22/2004 9:30 AM)

- Oregon. The Oregon Influenza Vaccine Education and Prioritization Plan 2004-05. A plan triggered by the influenza vaccine shortage aimed at avoiding health consequences for persons in high-risk groups for complications from influenza. Issued on October 8, 2004 by the Oregon State Health Officer. The plan consists of: 1) guidelines for healthcare providers; 2) rules for imposing civil penalties for violation of the guidelines; 3) mobilizing public and private health resources; and 4) notifying health professional boards of violations. This Plan is effective immediately, October 8, 2004, and will stay in effect through March 31, 2005, unless otherwise amended or rescinded. Authority cited: Oregon Revised Statute 433.040.
  (PDF file)
  (Posted: 10/13/2004 10:00 AM)

- Rhode Island. Influenza Outbreak Plan 2004-2005. A plan prepared by the Rhode Island Department of Health that outlines actions that were taken within the Department to prepare for the 2004-2005 influenza season.
  (PDF file)
  (Posted: 11/15/2004 1:30 PM)

- South Carolina. Public Health Advisory. Issued by the S.C. Department of Health and Environmental Control, regarding the prioritization and administration of the flu vaccination. (National Association of City and County Health Officials).
  (Web link)
  (Posted: 10/21/2004 10:00 AM)

- Vermont. Health Order. An order called by the Vermont Commissioner of Health for all health care providers and pharmacists to cease distributing and administering the influenza vaccine to anyone who is not in a high-risk category.
  (PDF file)
  (Posted: 10/22/2004 12:00 PM)

- Washington. King County's Flu Vaccine Health Order. A health order issued by the Director and Health Officer of Public Health, Seattle & King County directing health care providers and other vaccinators to only provide influenza vaccine to those at high risk.
  (Web link)
  (Posted: 10/13/2004 3:00 PM)

- Wisconsin. Wisconsin Emergency Order. An Emergency Order signed by the Department of Health and Family Services Secretary Helene Nelson mandating that flu vaccinations are limited to those individuals in the high priority group, and imposes penalties for noncompliance. (The National Association of County and City Health Officials).
  (PDF file)
  (Posted: 10/18/2004 3:00 PM)

State Attorney Generals File Suits Against Flu Vaccine Price Gouging

- Connecticut. A Complaint filed by the Connecticut Attorney General against flu vaccine distributor Meds-Stat for alleged price gouging.
  (PDF file)
  (Posted: 10/25/2004 11:00 AM)

- Florida. A Complaint and application for preliminary relief filed by the Florida Attorney General against flu vaccine distributor Meds-Stat.
  (PDF file)
  (Posted: 10/25/2004 11:00 AM)

- Kansas. A Press Release announcing that the Kansas Attorney General Office reached a settlement with Florida based Meds-Stat flu vaccine distributor.
  (Web link)
  (Posted: 11/15/2004 11:00 AM)

- Kansas. A Press Release from the Kansas Attorney General announcing a suit against Meds-Stat for alleged price gouging.
  (Web link)
  (Posted: 10/25/2004 11:00 AM)

- Texas. A News Release reporting that the Texas Attorney General filed suit against two distributors of flu vaccine for allegedly charging exorbitant prices.
  (Web link)
  (Posted: 10/25/2004 11:00 AM)

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IMMEDIATE RELEASE

October 15, 2004

Department of Health Issues Flu Vaccine Emergency Rule

(Washington, DC) Gregg A. Pane, MD, Acting Director of the DC Department of Health, issued an Emergency Rule mandating that available influenza vaccine held by District health care providers be used for priority groups only.

This emergency rule will enable us to more effectively follow the CDC recommendations that any available flu vaccine goes only to those who need it most, including the very young, the elderly, those with chronic medical conditions, and medical personnel who work directly with patients. It will ensure that we direct all available vaccine to our most vulnerable populations who have the highest risk for flu-related complications.

"In light of the nationwide and local shortages of vaccines for influenza, any available vaccine is to be given only to patients in high risk groups," said Dr. Pane.

The priority groups include:

- All children aged 6-23 months
- Adults aged 65 years and older
- Persons aged 2-64 years with underlying chronic medical conditions
- All women who will be pregnant during the influenza season
- Residents of nursing homes and long-term care facilities
- Health-care workers involved in direct patient care and
- Out-of-home caregivers and household contacts of children aged less than 6 months

The emergency rule on influenza vaccine is below.

NOTICE OF EMERGENCY RULEMAKING

The Acting Director of the Department of Health, pursuant to the authority set forth in section 3(a) of the Preventive Health Services Amendments Act of 1985 ("Act"), effective February 21, 1986, D.C. Law 6-83, D.C. Official Code § 7-131(a) and Mayor's Order 98-141, dated August 20, 1998, hereby gives notice of the adoption, on an emergency basis, of an amendment to Chapter 2 of Title 22 of the District of Columbia Municipal Regulations (DCMR) (Public Health and Medicine)(August 1986). This emergency rule requires health care providers to limit distribution of influenza vaccine during the 2004 to 2005 influenza season to only those persons in high risk categories. Emergency action is necessary because there is a temporary shortage of vaccine such that existing stocks of vaccine are not sufficient to distribute it to otherwise healthy individuals. To ensure that as many high risk persons as possible receive the vaccine it is necessary to take emergency action to restrict distribution of vaccine only to those high risk individuals.

The emergency rulemaking was adopted on October 14, 2004, and became effective immediately on the date of adoption. The emergency rules will expire February 11, 2005.

Chapter 2 of Title 22 DCMR is amended by adding two new sections 219 and 220 to read as follows:

219 Temporary Control of Influenza Vaccine

219.1 Due to a shortage of influenza vaccine during the 2004-2005 influenza season, health care providers shall administer influenza vaccine until February 11, 2005, only as follows:

a. To children aged six (6) to twenty-three (23) months
b. To adults aged sixty-five (65) years or older
c. To persons aged two (2) to sixty-four (64) years with underlying chronic medical conditions
d. To women who are pregnant
e. To residents of nursing homes and long-term care facilities
f. To children aged six (6) months to eighteen (18) years on chronic aspirin therapy
g. To health care workers involved in direct patient care; and
h. To out-of-home caregivers and household contacts of children younger than six (6) months of age.

220 Penalty

220.1 Any person who willfully does not comply with the influenza vaccine distribution requirements in section 219 shall be guilty of a misdemeanor and, upon conviction, subject to a fine not to exceed one thousand dollars ($1,000).

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30333

DEC 22 2004

The Honorable Tom Davis
Chairman, Committee on
Government Reform
House of Representatives
Washington, D.C. 20515-6143

Dear Mr. Chairman:

Thank you for giving me the opportunity to provide you with additional information regarding the efforts the Centers for Disease Control and Prevention (CDC) has undertaken to plan and prepare for an influenza pandemic. Many influenza experts, including those at CDC, consider the current threat of an influenza pandemic to be high. In particular, the epizootic of avian influenza A (H5N1), of unprecedented size in Asia, poses a greater risk for a pandemic than at any time in the recent past. Unfortunately, because of the nature of this epizootic, the probability of eradicating H5N1 from the bird populations of affected countries and getting this epizootic under control is low. Although the timing and impact of an influenza pandemic is unpredictable, the occurrence is likely and potentially devastating.

To prepare for such an event, we must implement activities to prepare for a pandemic influenza outbreak as well as enhance the nation's capacity to effectively respond to individual and public health needs that arise during annual, non-pandemic influenza seasons.

In this regard, CDC has undertaken several efforts to support influenza preparedness and response, including the following:

- CDC worked with the National Vaccine Program Office and other federal partners to develop the national Pandemic Influenza Preparedness and Response Plan. The goal of this plan is to limit the total burden of disease (morbidity and mortality) caused by an influenza pandemic and to reduce associated social disruption and economic loss. Objectives include strengthening global and domestic surveillance, enhancing public health and healthcare system readiness, and conducting research to improve influenza vaccines and other preventive interventions. The plan will be updated and revised regularly.

- In collaboration with the Council of State and Territorial Epidemiologists, CDC assists state and local public health and emergency management agencies in developing their pandemic influenza plans. A software program, FluAid, 2.0, that estimates the number of pandemic-associated deaths, hospitalizations, and outpatient visits, was made available to help state and local public health officials and policymakers prepare for the next influenza pandemic.

Another software program, FluSurge, helps planners calculate the potential burden of an influenza pandemic on healthcare resources (e.g., number of hospital beds required and doctors available to see outpatients as a percentage of existing capacity). Finally, CDC has developed pandemic influenza tabletop exercise materials to assist states and local areas in pandemic influenza planning.

- CDC has helped strengthen the World Health Organization's (WHO) global influenza surveillance system by providing support to expand the surveillance networks and conduct training in epidemiology, laboratory techniques, and biosafety. CDC also provided bilateral support to nine Asian countries affected by avian influenza to develop in-country networks for expanding geographic coverage of influenza surveillance. In both of these efforts, the integration of laboratory and epidemiologic data are emphasized. New partnerships with the Department of Defense (DOD) program in Jakarta and enhanced support to the International Emerging Infectious Disease Program in Thailand build on the current infrastructure to assess the impact of human and avian influenza viruses. Lastly, CDC staff have been strategically assigned to WHO offices in Vietnam, the Philippines, and Geneva to strengthen the partnership with WHO, enhance efforts in the field, and improve coordination among programs conducting surveillance for influenza among human and animal populations. This multi-faceted approach will foster long-term, year-round influenza surveillance for variant viruses that could circulate in the United States in the future and will enhance international capacity to identify human infections caused by viruses with pandemic potential.

- Through its Epidemiology and Laboratory Capacity (ELC) grant program, CDC has helped strengthen influenza laboratory diagnostic and response capabilities in 47 states and/or cities. CDC also has improved readiness by conducting training in molecular techniques for rapid identification of both human and avian influenza viruses, including H1, H3, H5, and H7, for 31 states. This ongoing training effort will enhance the U.S. capacity for early identification of viruses with pandemic potential and increase the speed with which influenza viral reporting occurs within states. Training for the remaining states is planned. In addition, efforts to enhance the U.S. influenza sentinel physician system and mortality surveillance systems are under way to develop better and more real-time estimates of the impact of influenza.

- CDC works with WHO to coordinate international efforts to develop influenza vaccine candidates. CDC has contributed to these efforts by producing reassortant pandemic vaccine candidate viruses against avian influenza A/H5 virus subtypes and influenza A/H9 and by conducting critical safety testing of potential influenza vaccine candidates. CDC has also identified key cell surface receptors that contribute to the decline in immune function in the elderly. In addition, CDC has established important collaborations with DOD to conduct a half-dose study and begin studies to look at other dose-sparing strategies and has developed partnerships with private industry and academia to evaluate new vaccine strategies. This research agenda is expected to lead to the development of more effective vaccines to protect against influenza.

- For the first time ever, the U.S. government has created stockpiles of both influenza vaccine and antiviral medications. The Department of Health and Human Services 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. In addition, the Strategic National Stockpile invested $87.1 million to stockpile 2.3 million doses of Oseltamivir and invested $34 million on Rimantadine capsules to treat 4.25 million adults and Rimantadine syrup to treat 750,000 children. These stockpiles give the government new ability to protect the most vulnerable groups of the U.S. population and respond effectively when there is a shortage of vaccine.

In addition, steps taken to respond to this year's inactivated influenza vaccine shortage helped enhance the nation's capacity for a pandemic response. For example, a secure data network, the Flu Vaccine Finder, was implemented to allow state health officials to identify all doses of trivalent inactivated influenza vaccine shipped to their state during the 2004-2005 season. Guidelines for large-scale influenza vaccination clinics were provided to the states. Other guidance documents that could be used in a pandemic, such as the use of masks to control influenza transmission, were also developed.

CDC will continue to work with its partners to enhance preparedness for an influenza pandemic based on the National Preparedness and Response Plan. Areas of future attention include providing increased technical assistance to states for pandemic planning, including a series of regional meetings on pandemic influenza planning; ensuring a supply of antiviral drugs; improving the adult immunization infrastructure; conducting epidemiologic studies to better understand the impact of influenza, both human and avian; initiating new studies to better understand immune function for improving vaccines, evaluate novel vaccine strategies, assess antigen sparing techniques to expand the availability of vaccine in a pandemic, and develop additional vaccine candidates for other potential threats; continuing to support the expansion of international surveillance; and developing a hospital surveillance system to monitor more severe cases of influenza.

These activities demonstrate CDC's leadership role in carrying out a coordinated and comprehensive program to strengthen our nation's preparedness for influenza outbreaks, including an influenza pandemic. Thank you again for giving me this opportunity to further describe our work in this important area of public health. Please do not hesitate to contact me should you need additional information.

Sincerely,

Julie Louise Gerberding, M.D., M.P.H.
Director

In 2003, 56% of the childhood vaccine doses were purchased by the public sector through federal contracts.

The slide below shows that:

9% were purchased through the discretionary 317 Immunization Grants appropriated by Congress

42% were purchased through the VFC entitlement program.

States that use their own funds to purchase vaccine do so through the federal contact and receive the benefits of negotiated prices. Therefore even though state funds purchased only 5% of vaccines, these were purchased through the federal contract.