THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

February 2, 2010

The Honorable Charles E. Grassley
United States Senate
Washington, D.C. 20510-6200

Dear Senator Grassley:

Thank you for your letter regarding 2009 H1N1 influenza virus vaccines. I appreciate your continued interest and engagement in the H1N1 influenza response effort. Answers to the specific questions you raised in your letter are provided below.

1. What criteria were used to select the five companies that are currently manufacturing the 2009 H1N1 influenza virus vaccines?

A decision was made at the beginning of the 2009 H1N1 outbreak to engage all five U.S.-licensed influenza vaccine manufacturers, three of which were already under contract with HHS for H5N1 vaccine production, to provide the greatest flexibility with respect to the amount and types of H1N1 vaccine supplied to the public.

a) How many companies submitted bids?

All five U.S.-licensed influenza vaccine manufacturers agreed to contracts for H1N1 vaccine production. The three companies already under contract – Sanofi Pasteur, Novartis, and GlaxoSmithKline (GSK) – agreed to contract modifications that allowed them to produce H1N1 vaccine for the public. The two vaccine manufacturers that were not already under contract – MedImmune and Commonwealth Serum Laboratories (CSL) – were offered the opportunity to enter into a contract for H1N1 vaccine production and both received a contract.

b) If more than five companies submitted bids, what were the reasons for rejecting the other bids?

There were no rejected bids.

2. How many doses of each vaccine have been purchased by HHS to date?

To date, HHS has ordered 229 million doses of bulk vaccine (vaccine concentrate) from the five vaccine manufacturers, including 25 million doses for international donation. The manufacturers have completed production of all the bulk H1N1 vaccine. We don't plan to fill and finish all 229 million bulk doses in vials, syringes, and sprayers. We are in the process of making final decisions about how much of the remaining bulk vaccine to fill and finish.

3. What is the total amount being paid to each of the five companies for their vaccines?

To date, orders in the following amounts have been placed with the manufacturers for bulk H1N1 vaccine and filling of the H1N1 vaccine. The manufacturers have completed all bulk H1N1 vaccine production. Over 70 percent of the filling orders have been completed.

Vaccine Manufacturer	Total Orders Placed
CSL	$91.1 million
GSK	$41.5 million
MedImmune	$452.5 million
Novartis	$492.4 million
Sanofi Pasteur	$513.4 million

a) How much has been paid as of the date of this letter?

The manufacturers submit their invoices for payment upon completion of work, release, and acceptance by the U.S. Government. The total amount that has been invoiced to date is approximately $1.2 billion.

4. When will the clinical trials on the H1N1 vaccines that were already underway in September be completed?

Beginning in August 2009, the National Institute of Allergy and Infectious Diseases (NIAID) within the National Institutes of Health (NIH) initiated a series of clinical trials to evaluate the dosage and number of doses of 2009 H1N1 influenza vaccine needed to induce a potentially protective immune response in a variety of populations, including healthy adults, the elderly, children, and pregnant woman. The focus of NIAID's efforts in undertaking these clinical trials was to generate and release data on the 2009 H1N1 vaccine in these populations as soon as it was available to help inform the decisions on the dosage of the vaccine in these populations.

For practical decision-making purposes, many of these trials can be considered complete – the participants have received their vaccinations, and preliminary data have been analyzed; the remaining ongoing trials will be completed in the spring of 2010. Over the past several months, NIAID has released key data on the safety and immunogenicity of the 2009 H1N1 vaccine that supported the need for one vaccine dose in adults, the elderly, and pregnant women, and two doses in children under 10 years old. The full data will be analyzed to provide a complete and accurate understanding of the safety and immunogenicity of the vaccines. The final analysis of the data from all of the clinical trials is expected to take several more months.

a) Are there additional findings to date regarding the adverse event profiles of any of the five vaccines?

HHS monitors adverse events through a number of passive and active surveillance systems. For H1N1 vaccine safety monitoring, existing vaccine safety infrastructure was enhanced, and new infrastructure was created specifically to ensure a more robust vaccine safety monitoring system for H1N1 influenza vaccines. Additional information about these systems may be found at http://flu.gov/professional/federal/monitor_immunization_safety.html. One important component of federal vaccine safety monitoring is the Vaccine Adverse Event Reporting System (VAERS), a passive reporting system cosponsored by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). As of December 30, 2009, VAERS had received 7,326 adverse event reports following 2009 H1N1 vaccination. The vast majority (94%) of adverse events reported to VAERS after receiving the 2009 H1N1 vaccine are classified as "non-serious" (e.g., soreness at the vaccine injection site). For the 2009 H1N1 vaccine, the percentage of reports involving what would be considered serious health events does not differ from the percentage reported for seasonal influenza vaccines. Active surveillance systems use rapid cycle analysis to investigate pre-specified outcomes of interest as well as emerging issues should they arise. No unexpected adverse events or patterns of adverse events have emerged.

Additionally, the National Vaccine Advisory Committee's (NVAC) Vaccine Safety Risk Assessment Working Group (VSRAWG) was formed with the charge to conduct independent, rapid reviews of available safety monitoring data for the 2009 H1N1 influenza vaccines. The VSRAWG's first report was approved unanimously by the NVAC on December 16, 2009. In the report, the VSRAWG concluded that "the data do not favor a signal between the outcomes examined and the H1N1 vaccines. A signal is defined as an event that could be temporarily occurring more often after vaccine receipt than anticipated by chance alone. The evidence for this includes:

1. No serious adverse events (SAEs) have been attributed to the H1N1 vaccines in the clinical trials to date.
2. Comparison of reporting in the Vaccine Adverse Event Reporting System (VAERS) of SAEs after seasonal and other similar vaccines and H1N1 influenza vaccines generally show similar levels of SAEs.
3. For those systems conducting rapid cycle analysis, the rates of adverse events for pre-specified outcomes, including Guillain Barré syndrome, are within expected values.

The VSRAWG presented its second report to the NVAC on January 20, 2010. Reports of the VSRAWG are available at http://www.hhs.gov/nvpo/nvac/reports/index.html.

5. In light of the two recalls last month, what are HHS, CDC, FDA and the vaccine manufacturers doing to ensure the potency of the vaccines to be delivered in the coming months?

Both manufacturers of the recalled lots have conducted investigations to determine the cause of the potency failures of these H1N1 vaccines. MedImmune has made an adjustment to its vaccine to ensure the potency of the vaccine for the 18 weeks as licensed and is able to continue production without further concerns. Sanofi Pasteur is still working through its root cause analysis to understand the cause of the potency failure in its pediatric vaccine. Until the root cause is known, Sanofi Pasteur will be unable to produce its pediatric H1N1 vaccine in single-dose pre-filled syringes. Sanofi is continuing to monitor its vaccine reserved for stability testing.

As you may know, on January 29, Sanofi Pasteur announced a second recall involving five lots of single-dose, pre-filled syringe pediatric vaccine and one lot of single-dose pre-filled syringe for older children and adults. As with the two recalls described above, as part of routine testing, the manufacturer found that the potency of the lots in question had fallen below pre-specified levels.

It is important to note that these are non-safety-related recalls, and both CDC and FDA believe the recalled H1N1 vaccine to be effective in stimulating a protective response despite the slight reduction in the concentration of antigen.

In addition, FDA has reviewed stability and potency data for the monovalent H1N1 vaccine manufactured by other U.S. licensed influenza vaccine manufacturers to ensure compliance with potency specifications. Representative samples of each vaccine formulation are also undergoing real-time stability analysis, which includes testing for potency.

a) Last week, a press report stated that "truckloads of swine flu vaccines" were being returned in New York State because there was not as much demand for the vaccine as expected. Are there plans to check the potency of the returned vaccines?

The report in question stems from a misunderstanding within New York State that resulted in excess vaccine being shipped to certain sites that had ordered vaccine. This communication breakdown has since been resolved. These vaccines were shipped out with temperature monitors -- if the monitors showed that the vaccine was held at the proper temperature during shipment and return, the vaccine was returned to inventory. There have been a few cases where vaccine has been returned that was not held at the proper temperature; in those limited cases, the vaccine was discarded.

b) What is the expected shelf life of the H1N1 vaccines?

CSL and GSK H1N1 vaccines have an expiration of June 30, 2010. For H1N1 vaccine produced by MedImmune, the expiration date is 18 weeks from the date of manufacture. For Novartis, it is six months from the date of manufacture. For Sanofi Pasteur, it is 18 months from the date of manufacture.

6. How many manufacturing facilities have been approved by the FDA for production of the H1N1 influenza virus vaccines?

The FDA-approved 2009 H1N1 monovalent vaccines were made in the same licensed facilities and with the same manufacturing processes used to safely produce seasonal influenza virus vaccine every year. In addition, since May 2009, FDA has approved six supplements to the existing licenses for Sanofi Pasteur, CSL, Novartis, and MedImmune for new manufacturing facilities. There are five licensed manufacturers of 2009 H1N1 vaccine. Three of the five have domestic production facilities. Four of the five manufacturers have foreign production facilities.

a) How many times have each of these facilities been inspected to ensure good manufacturing practices?

We subject the 2009 H1N1 influenza vaccines to the same stringent manufacturing and quality oversight processes in place for seasonal influenza vaccine. FDA inspects these plants – both domestic and foreign – at least once each year to ensure that quality controls are followed at every step in the production process. Each facility is also inspected annually for compliance with FDA's current Good Manufacturing Practice regulations. Extensive in-process quality control and product testing (such as for potency and purity) are required at multiple stages of the manufacturing process. No lot of the 2009 H1N1 vaccine can be used until it has been fully tested and released as sterile and potent by both the manufacturer and FDA. In the case of the recalled lots described in question 5, they passed potency testing initially and experienced unexpected drops in potency during storage. In addition, FDA performs pre-approval inspections of new influenza virus vaccine facilities as part of the review process.

b) On what dates were those inspections conducted and what were the findings of the inspections?

Each of the already-licensed facilities, domestic and foreign, was inspected at least once in 2009, and the inspections were conducted on numerous dates between spring and fall. There were no findings that resulted in the need for agency action for any of the facilities inspected.

7. On June 25, 2009, HHS extended the Public Readiness and Emergency Preparedness Act declaration for pandemic vaccines, to include H1N1 vaccines, which provides immunity from tort liability to individuals and entities involved in the manufacture, distribution, and administration of the H1N1 vaccines. What oversight is in place to ensure that the individuals and entities covered by the amended declaration manufacture, distribute, and/or administer the vaccines as intended and legally authorized?

The Public Readiness and Emergency Preparedness (PREP) Act provides immunity (except for willful misconduct) from tort liability claims arising from administration and use of covered countermeasures to the United States, manufacturers, distributors, states, local governments, tribes and other public and private program administrators, and health care professionals. HHS has a number of oversight mechanisms in place to ensure that covered persons utilize the covered

countermeasures as intended. FDA-regulated entities, including vaccine manufacturers, are subject to FDA inspectional and compliance activities and to FDA's ongoing efforts to ensure compliance with the applicable authorities that the agency administers. The vaccine distribution process for the H1N1 monovalent vaccine is administered by CDC, and includes numerous oversight mechanisms. CDC works with the vaccine distributor to ensure that appropriate standards for transport, storage, and distribution are being met, and provides guidance and technical assistance to states, local governments, tribes, territories, other public and private program administrators, and health care professionals to ensure that the vaccine is being administered as intended.

8. A shortage of seasonal flu vaccine was reported in November. I understand that at that time, there were still about 24 million doses yet to be shipped.

a) What is the status of the 24 million doses?

In November, one vaccine manufacturer experienced a delay in the release of a certain amount of seasonal flu vaccine; however, it is our understanding that all of this vaccine was distributed by the end of November. It is important to note that seasonal influenza vaccine production and distribution in the United States is managed primarily by the private sector.

b) Did the commitment from five of the seasonal flu vaccine manufacturers to manufacture the H1N1 vaccine contribute to the seasonal flu vaccine shortage?

No, the commitment from the five seasonal flu vaccine manufacturers to manufacture the H1N1 vaccine did not contribute to the seasonal flu vaccine shortage. Seasonal flu vaccine production for the 2009-2010 season lasted longer than usual, into mid-October, because of production problems with one of the seasonal flu vaccine strains. There also was a brief interruption (now resolved) in operation of new fill-finish production lines put in place to handle the greatly expanded demands to fill both seasonal and 2009 H1N1 vaccines, resulting in delayed vaccine production from these lines by about one month. HHS worked closely with the manufacturers to minimize the impact of these delays. Additionally, although production and distribution of the 2009 H1N1 vaccine is distinct from the seasonal flu vaccine, the publicity surrounding the H1N1 vaccine resulted in increased public awareness of vaccination, which in turn led to an increased demand for seasonal flu vaccine. This increased demand impacted the immediate availability of vaccine in some areas.

c) What steps are being taken to prevent severe seasonal flu vaccine shortages in the future?

Unlike H1N1 vaccine, which was purchased entirely by the U.S. government, only a small portion of seasonal influenza vaccine is purchased by the U.S. government. Matching supply to demand for seasonal influenza vaccine is much more challenging

for manufacturers. They deal with a much more complicated market of purchasers, and are at financial risk when they produce seasonal vaccine in excess of actual demand. By encouraging seasonal influenza vaccination, the U.S. government contributes in the long term to a growing market for seasonal vaccine.

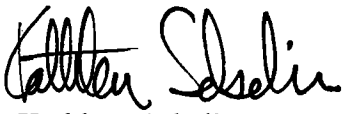
On November 27, 2009, FDA approved Agriflu, an inactivated trivalent seasonal influenza vaccine made by Novartis for ages 18 years and older to prevent disease caused by influenza virus subtypes A and B. Agriflu is not intended to protect against the 2009 H1N1 influenza. This approval further increases the influenza vaccine capacity for the U.S., both for seasonal influenza vaccines as well as for influenza vaccines for future pandemics. This increased the number of U.S.-licensed seasonal influenza vaccine products to seven, compared with three in 2004.

Furthermore, major investments are underway in advanced vaccine development and manufacturing capacities, which include vaccines manufactured in cell culture systems. FDA has provided guidance to manufacturers to help ensure that cell culture-based vaccines can be made safely. In addition, we are supporting the development and use of recombinant and other newer technologies that offer the potential to serve as "platforms" for more rapid development, production, and deployment of vaccines against new influenza viruses or other emerging public health threats. Ongoing scientific efforts at NIH and FDA are evaluating even more advanced approaches, such as DNA vaccines and "universal" influenza vaccines, which potentially may protect against multiple and evolving influenza strains. These approaches may offer a number of advantages in scalability, reliability, and speed.

In addition, HHS is funding the development and careful evaluation of adjuvanted influenza vaccines. Adjuvants are immune enhancers, and studies have shown that when an adjuvant is used, a lower dose of the vaccines can produce the same immune response as the full dose of the vaccine alone.

Again, thank you for your letter. I appreciate your strong commitment to public health preparedness and look forward to continuing to work with you on these important issues.

Sincerely,



Kathleen Sebelius