

Statement of Paul Perreault
President, CSL Biotherapies, Inc.
Before
The Energy and Commerce Subcommittee on Oversight and Investigations and the
Subcommittee on Health
Concerning
H1N1 Influenza Vaccine Preparedness

November 18, 2009

Good morning Mr. Chairman and members of the committee. I am Paul Perreault, President of CSL Biotherapies Inc., the U.S. distributor of influenza vaccines manufactured by our parent company CSL Limited, located in Melbourne, Australia. I am pleased to be here today to discuss our experience in manufacturing the H1N1 vaccine specifically for the United States. We believe it is important to understand how the government and industry can best work to help assure vaccines for influenza pandemics.

I want to assure this committee that CSL Biotherapies, Inc. is committed to providing the entire amount of both the H1N1 bulk antigen and the finished vaccine doses that we have committed to in our contract with the Department of Health and Human Services (HHS). We take the H1N1 pandemic very seriously and have been a leader in developing and delivering a vaccine against it.

About CSL Limited

CSL is a leading global biopharmaceutical company with headquarters in Melbourne, Australia. The company researches and manufactures vaccines and therapies for rare and serious conditions. CSL originated in 1916 when it was formed to provide vaccines and therapies to the Australian population. It now has a presence in 27 countries with worldwide research and manufacturing. The company has a major manufacturing facility in Kankakee, Illinois and its headquarters in King of Prussia, Pennsylvania for CSL Biotherapies, Inc. and CSL Behring, CSL's global plasma therapies division for rare conditions such as hemophilia, primary immune deficiency and genetic emphysema.

CSL Seasonal Flu Vaccine Production for the United States

CSL has manufactured vaccines since its beginning. As CSL grew, we were able to provide influenza vaccines in more countries; first in the southern hemisphere and more recently in the northern hemisphere. Our world class influenza vaccine production facilities have the capacity to produce up to 80 million doses of trivalent seasonal influenza vaccine annually.

Our seasonal flu vaccine, Afluria™ was launched in the United States in October 2007. Afluria™ was first indicated for ages 18 and above in the United States. I am very

pleased to report that Afluria™ received approval on November 10, 2009 for administration to individuals six months through 17 years of age. The same indication was provided simultaneously for our H1N1 vaccine.

Afluria™ is manufactured at our facility in Melbourne, Australia. However, fill and finish of our vaccine for the United States – where we finish the vaccine doses and “fill” them into pre-filled single dose syringes or multi-dose vials - is being performed in a newly licensed, state of the art syringe filling line in Kankakee, Illinois and a modern facility in Marburg, Germany. Pre-filled syringes of Afluria come in a thimerosal-free formulation.

In late September 2009, CSL Biotherapies entered into an agreement to license sole distribution rights of Afluria™ to Merck in the United States, which further assures the distribution of this valuable vaccine in this country.

CSL Production of H1N1 Vaccine for the United States

CSL is committed to providing H1N1 vaccine. CSL initiated the western world’s first human trials with a 2009 H1N1 vaccine, and published research findings in the *New England Journal of Medicine* (Greenberg ME et al, NEJM 2009; 361), that had a major impact informing vaccine policy globally. The interim findings of this trial were the first to establish that a single 15 microgram dose of the unadjuvanted vaccine was well-tolerated and highly immunogenic in adults. This helped establish the policy that only one dose of the vaccine would be needed instead of two doses as had been presumed. These data, along with results of clinical trials in infants and children were communicated rapidly to regulatory and public health authorities in the United States and globally, recognizing their value to public health decision-making.

In May 2009, the Office of the Biomedical Advanced Research and Development Authority (BARDA) approached CSL Biotherapies to inquire about whether we might be able to provide an H1N1 vaccine for the United States. CSL Biotherapies worked with BARDA and entered into a one-year special contract, initiated on May 28, 2009 to provide 36 million dose equivalents of H1N1 bulk antigen to the United States government for the 2009-10 flu season (CSL did not have a previous pandemic contract with the United States government). As part of this agreement, CSL made it clear that we had a pre-existing contractual obligation with the Australian government to provide vaccine to Australia first, should the World Health Organization declare a pandemic, which it did. I must stress that CSL Biotherapies’ commitment to Australia in no way impacted our schedule to provide vaccine to the United States.

Our initial estimates for 2009 H1N1 vaccine production capacity were based on several factors: expected yields for the novel H1N1 flu strain based on our prior experience producing H1N1 influenza virus strains; timing, logistics and plans to shift our manufacturing from seasonal influenza vaccine for the Northern Hemisphere to novel H1N1 vaccine production as a monovalent vaccine. We carefully analyzed our capacity based on expected yields and the ability to process 300,000 eggs per day.

Delivery of H1N1 bulk antigen was impacted versus original estimates due to lower yield for this novel strain of H1N1 versus previous H1N1 seasonal influenza strains. It must be understood that the production of influenza vaccine is a biological system and as such the speed of availability of vaccine doses is often more related to the ability of the virus to be grown in the chosen substrate (whether eggs or cells) than any other constraint. It is not always possible to ensure the virus will grow well.

Difficulties with the H1N1 Vaccine Seed

On June 1, 2009, CSL received the first H1N1 virus vaccine seed from the New York Medical College. CSL began developing a seed lot and bulk manufacturing activities on June 19. CSL observed lower than expected yields. The yields were approximately one third to one half of an average H1N1 seasonal influenza yield. As a result of these low yields a revised delivery schedule was created and sent to HHS on July 2, 2009.

CSL promptly initiated a program to investigate improvements to yields including egg incubation temperatures and inoculation concentrations. CSL made a number of incremental improvements to the manufacturing process, resulting in a yield improvement of 10% over that obtained using the initial virus vaccine seed lot.

On August 18, 2009, CSL received a new vaccine virus seed from the New York Medical College that was introduced into the manufacturing process on September 4, 2009. Yield improvements in excess of 80% compared to the previous seed were observed in the initial lots using indicative in-process measurements. Manufacturing of H1N1 bulk antigen is in progress according to a revised supply plan sent to HHS on September 14, 2009. On October 30, 2009, CSL provided the latest delivery schedule to HHS with an increase in the finished dose output volumes.

CSL remains committed to maximizing the yield and availability of the H1N1 virus vaccine. To this end, improvement projects, such as optimizing incubation conditions and inoculation concentrations, are continuing within the manufacturing area. CSL also invested in fill and finish facilities in both Europe and the U.S. to improve availability of seasonal and pandemic influenza vaccine and achieved licensing of our U.S. facility for fill and finish this year, working closely with FDA.

I would like to take this opportunity to highlight the cooperation that CSL Biotherapies, has experienced with BARDA. This agency has worked collaboratively to put in place the original contract and has stayed in close touch throughout the seed lot and production schedule changes. I am in frequent contact with the BARDA staff. BARDA's and HHS' focus and sense of urgency in bringing H1N1 to the United States aided CSL's ability to deliver H1N1 vaccine to the United States.

Cell Based Versus Egg Based Vaccine Technology

Because egg-based technology has been in existence for some time, there are some misconceptions that egg-based vaccine technology is outdated and somehow might be responsible for slower production of H1N1 vaccine. CSL uses and continues to believe in egg-based technology. We use this technology for both our seasonal flu vaccine and for the H1N1 vaccine. There is nothing different about the H1N1 vaccine manufacturing process compared to that of regular seasonal flu vaccine, except for the virus strain.

In the past 3 to 4 years, CSL Biotherapies, Inc. and other major manufacturers have invested heavily in expanding egg based production capacity. All seasonal influenza vaccine used in the U.S. and the vast majority of that used in the rest of the world, is derived from egg based manufacturing.

The misconceptions surrounding egg versus cell technology include the following:

i) Production is limited by availability of eggs

In Australia, at CSL, manufacturing occurs for both northern and southern hemispheres. Eggs are available all year round and have not constrained our production.

ii) Time is lost in developing suitable seed virus for manufacture in eggs

It is true that some time is required to achieve good production yields with many strains regardless of the medium. However, the record to date shows good production can be achieved in eggs far more reliably for difficult strains than in cell-based technology.

iii) Length of process is longer in eggs

Processing time is similar for eggs and cells.

iv) Cells can produce more efficacious vaccines

The performance of both CSL's vaccine and manufacturing system were clearly demonstrated in the recent H1N1 clinical trials conducted both in the U.S. and Australia. These trials, as referenced in the New England Journal of Medicine, illustrate the positive impact our H1N1 flu vaccine will have in protecting the population from the virus. These clinical trials were conducted with vaccine doses manufactured from egg based technology.

CSL has been conducting a development program in cell culture influenza vaccine manufacturing for a number of years. We have evaluated many different cell lines, and in our opinion, all have been shown to be unreliable in either performance at large scale or in yield of virus. None were as reliable as eggs in producing good yields for all strains.

More recently, CSL has evaluated a new cell line that we believe shows the most promise for reliable production. We are currently evaluating our options for this approach.

CSL believes it will be many years before cell culture is advanced and efficacious enough to challenge egg technology as the preferred means of production, even as we have engaged in exploring the possibility of cell-based production. We also believe that the technology currently used is well suited to ensuring the most rapid response to meeting U.S. requirements at this time.

Recommendations for Improvements in the System

Seed lots - I would recommend there be a focus on producing a greater assortment of influenza seed lots earlier that can be utilized in the creation of future pandemic influenza vaccines. As we have seen, the poor yields resulting from the first available seed lot had a significant effect on reducing the amount of available H1N1 vaccine. If, for instance, the 10-week gap in identifying the second, higher yield seed lots could have been avoided, manufacturing could have occurred sooner. This would be my first priority, and in my view supersedes any concerns about cell based versus egg based technologies.

New adjuvants - could help to enhance the immune response and reduce required dosing, which would make more antigen available for additional vaccinations. A supportive environment for development of new adjuvants with influenza vaccine could facilitate this advancement.

Increasing vaccination rates - more education programs about the benefits of influenza vaccination, to help address fear or apathy, and vaccination rate increases to come closer to CDC recommendations for whom should be vaccinated, would help to prevent influenza and support readiness.

Conclusions

Thank you again for the opportunity to speak before the committee and answer questions. I hope today's hearing provides more insight into the complex world of H1N1 vaccine production. CSL and CSL Biotherapies, Inc. are committed to working with the United States government to produce and provide H1N1 flu vaccine as quickly as possible. Our passion at CSL and CSL Biotherapies, Inc. is to help save and improve patient lives and we wish to do our part in protecting the US population and other parts of the world from H1N1 and seasonal influenza. We will continue to focus on this goal and work with government collaboratively to accomplish that.