FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS

EVALUATION AND RESEARCH

VACCINES AND RELATED

BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

November 19, 2009

Bethesda Marriott
5151 Pooks Hill Road
Bethesda, Maryland

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P R O C E E D I N G S (9:00 a.m.)

Agenda Item: Call to Order and Opening Remarks

DR. STAPLETON: I'd like to call this meeting to order. I am Dr. Jack Stapleton from the University of Iowa.

The first order of business is to ask our designated federal official Christine Walsh to make an announcement.

Agenda Item: Conflict of Interest Statement

MS. WALSH: Thank you, Dr. Stapleton. Good morning, everyone. Before I read the conflict of interest statement, I just have one correction to the agenda today. If you will look at today's agenda, you will see that Dr. John Modlin is listed as Chair, and of course Dr. Stapleton has introduced himself, so Dr. Jack Stapleton will be our Chair today.

This brief announcement is in addition to the conflict of interest statement read at the beginning of the meeting on November 18 and will be part of the public record for the Vaccines and Related Biological Products Advisory Committee meeting on November 19, 2009. This announcement covers conflicts of interest for topic three, the discussions and recommendations on the safety and effectiveness of an influenza vaccine purified recombinant influenza hemagglutinin, manufactured by Protein Sciences Corporation. This is a particular matter involving specific parties.

Based on the agenda and all financial interests reported by members and consultants, no conflict of interest waivers were issued in accordance with 18 USC 208b3 and 712 of the Food Drug and Cosmetic Act.

Dr. Margaret Rennels is serving as the industry representative, acting on behalf of all related industry. She is employed by GlaxoSmithKline in Washington, D.C. Industry representatives are not special government employees and do not vote. This conflict of interest statement will be available for review at the registration table.

We would like to remind members, consultants and participants that if the discussions involve any other product or firm not already on the agenda for which an FDA participation has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationship that you have with any firm that could be affected by the discussions.

Dr. Stapleton.

DR. STAPLETON: A couple of additional announcements. I would like to request that everyone please check your cell phones and pagers, make sure they are off or on silent mode. I would also like to request that any media

inquiries be directed to Pat El-Hinnawy from the FDA Office of Public Affairs.

I would like to welcome you this morning and ask the committee members to introduce themselves. We will start with Dr. McInnes. We will start with Dr. McInnes.

DR. MC INNES: I am Pamela McInnes, National Institutes of Health.

DR. WHARTON: Melinda Wharton, Centers for Disease Control and Prevention.

DR. SANCHEZ: Pablo Sanchez, University of Texas Southwestern Medical Center, Dallas.

DR. LEVANDOWSKI: Roland Levandowski. I don't have an institutional affiliation. I am an infectious diseases physician. I work as a volunteer for public health organizations.

DR. FLEMING: Thomas Fleming, University of Washington

DR. DEBOLD: Vicki Debold, National Vaccine Information Center.

DR. GELLIN: Bruce Gellin, National Vaccine Program Office, HHS.

DR. ROMERO: Jose Romero, University of Arkansas for Medical Sciences.

DR. RENNELS: Peggy Rennels, industry representative.

DR. DeSTEFANO: Frank DeStefano, Centers for Disease Control and Prevention.

DR. EICKHOFF: Ted Eickhoff, University of Colorado-Denver. Director of the Office of Vaccines Research in CBER, FDA.

DR. SUN: Wellington Sun, Division of Vaccines, CBER.

DR. NOLLETTI: Cynthia Nolletti, Medical Officer, CBER.

Agenda Item: Topic 3: Safety and Effectiveness of Influenza Vaccine, Purified Recombinant Infuenza Hemagglutinin

DR. STAPLETON: Thank you. Our first speaker this morning is Dr. Rakesh Pandey from the FDA. He will provide us an introduction.

Agenda Item: FDA Introduction/Presentation of Questions

DR. PANDEY: Thank you, Dr. Modlin. Good morning, everyone. I am Rakesh Pandey from CBER's Office of Vaccines. As the representative of the FluBlok BLA for Protein Sciences Corporation's license application for influenza vaccine, recombinant hemagglutinin, I welcome you all here this morning to the Vaccines and Related Biological Products Advisory Committee meeting. I am going to introduce the topic for today's discussion and say what this deal is about

and go over the agenda and the questions we have for the committee.

FluBlok, which is the subject of Protein Sciences Corporation's application, consists of 45 microgram each of purified recombinant hemagglutinin antigen from the three strains recommended for the seasonal influenza vaccine formulation, for a total of 135 microgram HA antigen per dose.

The hemagglutinin gene from the recommended strains is cloned in a baculovirus expression vector, and the recombinant hemagglutinin is expressed SF-9 and expresSF cell line which is derived from the fall armyworm, *Spodoptera frugiperda*.

Each .5 milliliter dose of the vaccine contains 45 microgram of each recombinant hemagglutinin antigen in sterile phosphate buffered saline containing .005 percent Tween 20. Since this is a single dose product which is supplied in single dose glass vials, they are stored at two degrees Celsius, being a single dose product it doesn't have any preservative. Also it is an unadjuvanted product. Also I would like to point out that this vaccine does not contain any neuraminidase antigen, and hemagglutinin is the only antigen in this vaccine.

Also, the indication that Protein Sciences is seeking for this product is for active immunization of adults

18 years of age and older against seasonal influenza disease caused by influenza virus subtypes A and type B represented in the vaccine.

While I am not going to go into the details of the clinical data in my brief introduction, I just want to mention here that the BLA for FluBlok contains data from four randomized well controlled clinical studies. One of them was a phase II study and there were three phase III studies in support of the 45 microgram per strain dose that Protein Sciences intends to market. Two of these studies were placebo controlled and the other two studies were active control trials that used a U.S. licensed inactivated influenza vaccine.

The total safety database for the application includes 3,233 FluBlok recipients, out of which about 23 percent were older than 50 years of age and about 13 percent were older than 65. For the vaccine efficacy, all of the 2,344 subjects in the study were between 18 to 49 years of age.

The database for the immunogenicity includes 1,323 subjects, out of which 55 percent were over 50 years of age and about 32 percent over the age of 65.

Obviously you will be hearing details on this data in the subsequent presentation. I would just like to present the regulatory history of this file in brief. The Protein

Sciences IND for this trivalent formulation was submitted initially on October 23, 2004. Subsequently they had requested a fast track, and on December 11, 2006, we granted a fast track for this product.

September 21, 2007, we had a pre-BLA meeting with Protein Sciences to discuss the modalities of submitting the BLA application. The following year on April 18, Protein Sciences submitted their BLA requesting accelerated approval.

In August of 2008, we issued a complete response letter, thereby stopping the review clock. Then in April of 2009 Protein Sciences submitted a complete response to CBER's complete response letter, and they also included additional data on the clinical efficacy that became available post the first round CRL letter.

This is the agenda for today's discussion following my introduction. There will be a sponsor presentation from Dr. Cox and Dr. Treanor. Thereafter there will be a short break, and that will be followed by Dr. Cynthia Nolletti's presentation of FDA's clinical review of the BLA. We are scheduled for lunch around 12:30. Following lunch when we reconvene, there will be an open public hearing, and that will be followed by a presentation of questions before the committee starts the discussion and gives its recommendations.

Leading up to the questions, these are the

questions we have for the committee today. You will be seeing these questions several times today during Dr. Nolletti's presentation and also before the committee begins its discussion and voting. So we wanted you to keep these questions in mind while the next presentations are going on.

The questions we have for the committee, the first question is, do the available clinical data support an indication for FluBlok in the prevention of influenza disease caused by influenza subtypes A and type B included in the vaccine in adults, A. 18 to 49 years of age, B, 50 to 64 years of age, C, 65 years of age and older.

The second question is, do the available safety data support the safety of FluBlok in adults 18 years and older?

The third and last question is, please comment on what additional studies, if any, should be requested postlicensure.

That is all I have. Thanks.

DR. STAPLETON: Thank you, Dr. Pandey. Are there any questions for Dr. Pandey before we move forward? If not, then our next speaker is Dr. Manon Cox from Protein Sciences.

Agenda Item: Protein Sciences Presentation

DR. COX: Welcome, everybody. We are very pleased that today the committee will consider FluBlok for advice.

I would like to start with a brief introduction. I

am very pleased and honored that Professor John Treanor from the University of Rochester is willing to present our clinical data. I will then wrap up again with a summary of the presentation.

As we have heard before, FluBlok is a recombinant hemagglutinin vaccine. It contains the dose that we have proposed is 135 micrograms of recombinant hemagglutinin, which means 45 micrograms per antigen, while the licensed vaccine contains 15 micrograms per antigen, to put that in perspective, and the vaccine does not contain an adjuvant.

The product is produced using a cell culture production process, so it is not dependent on inoculating eggs with live influenza viruses.

The main features of the product is that it is a purified protein, which allows us to pursue a high dose. In the early '90s, it was already shown by various manufacturers that high doses of influenza vaccines would lead to higher immunogenicity. This product does not contain egg proteins, and it has a low endotoxin content. Our production cycle is short, and we do not need to handle live influenza viruses or eggs.

The proposed indication as already shown by Dr. Pandey previously is, FluBlok is a recombinant hemagglutinin influenza vaccine indicated for active immunization of adults 18 years of age and older against seasonal influenza disease

caused by influenza virus subtypes A and type B represented in the vaccine.

As we all know, seasonal influenza is a highly contagious acute viral respiratory disease occurring seasonally and globally, and epidemics occur annually. This results in more than 220,000 excess hospitalizations and on average 36,000 excess deaths annually in the United States alone.

Over 90 percent of influenza related deaths occur in people 65 years and older. Children under five and pregnant women are as you know in their third trimester also at higher risk for severe complications of influenza.

The licensed influenza vaccine is a trivalent vaccine. It contains two A strains, H1 and H3, and a B strain. The protection of the vaccine correlates with the hemagglutinin in antibody, so this vaccine, its content is based on the amount of hemagglutinin that is present in the vaccine.

The production process, just in very brief summary. Chicken embryos are infected with an influenza virus. The virus is then isolated, and for the inactivated vaccines, the virus is subsequently killed and more or less purified, dependent on the formulation that we are looking at.

The licensed influenza vaccines have a number of potential disadvantages. It requires a relatively long

production cycle. We need to make high growth reassortants to be able to enter into the production process. This requires on average one egg to produce one dose of influenza vaccine. There are potential production issues possible with avian influenza outbreaks when egg supplies could be interrupted. You do need to adapt the seed virus, and the vaccine is less effective in the elderly. Besides that, probably most important, people that have egg allergies are usually contraindicated to take the vaccine.

The FluBlok composition once again. It is a trivalent seasonal vaccine with three full-length recombinant hemagglutinin proteins. A single dose contains 135 microgram of total recombinant hemagglutinin, 45 microgram of each strain. The protein is produced in expresSF, which I will further refer to as SF+ cells. These are caterpillar cells, as indicated by Dr. Pandey, without serum, using a viral vector called the baculovirus vector. Recently with the approval of Cervarix we have in the United States now the first protein vaccine or particle vaccine approved that is made in this production system.

The product is formulated without adjuvant, antibiotics or preservative. It is again a protein based vaccine with a low endotoxin content.

Very briefly, in this slide we see on the far left end a baculovirus. For those of you who are not familiar

with baculoviruses, if you eat green vegetables you consume about 10^{11}, 10^{12} baculovirus particles per day in an average portio of salad. What we do is, we engineer this baculovirus, which is a DNA virus with the gene of interest, in this case the recombinant hemagglutinin, and these baculoviruses are then highly specific for the cell line that we have established. We use a powerful DNA element promoter to direct the production of this protein.

One of the main challenges with influenza vaccine manufacturing is that this VRBPAC committee on an annual basis decides what the composition of the vaccine needs to be. That leaves the manufacturer with only four to six months time to develop a product that needs to be on the market in September or October.

In order to make a recombinant based product, you are dependent on a production process that will require one single cell line that is well characterized. Just to put this in perspective, it took us about two years to fully execute the characterization of our cell line. We use the same cell line for all our production processes, and the only thing that we modify from year to year or from strain to strain or protein to protein is the recombinant baculovirus.

So these cells are grown in big bioreactors. We infect these cells then with the engineered virus, and after about 60 hours we harvest the cells and purify the protein of

interest. This protein is then formulated in saline salts.

The potential advantages of this vaccine is that the vaccine composition is not constrained by selection or adaptation of an influenza seed virus. The cloning, expression and manufacturing of FluBlok can be completed in just two months. In fact, if you would have the recombinant baculovirus ready for production you could be releasing your first product within a month of starting manufacturing.

The product is produced in cell culture and does not utilize embryonated chicken eggs, and it does not require the availability of biocontainment facilities. We are not working with a virus that is harmful to human beings. We are not working with a live influenza virus. The high yield process allows an increased yield which we then as we will show later use to enhance immunogenicity.

This slide in somewhat more detail summarizes that manufacturing process for a trivalent influenza vaccine. If we receive the virus on day zero, about 30 days later we are ready to go into manufacturing. Our next work will be to reduce the time that is required for product release testing, because there is some product release tests that do have a long throughput time, such as mycoplasma or steroplasma.

While Dr. Pandey indicated that we filed our IND for a trivalent influenza vaccine in 2004, the development of this product really started many, many years before in

collaboration with NIH and NIAID. Starting in 1993 we performed nine clinical studies, initially with monovalent formulations of the influenza vaccine, and then later with trivalent formulations. Then in 2004 we felt that there was adequate data generated to support the development of this product. Dr. Treanor again will go into the details of these clinical studies.

In 2004-2005 we conducted study PSC01, which was a dose escalation study, and also had an efficacy component. Then in 2006-2007 we conducted a study in a little over 800 subjects older than 65 years of age, and in 2007-2008 we conducted two other studies, a large study in 18 to 49 years of age, where we looked at efficacy and immunogenicity, and a study in 50 to 64 years of age. We submitted our BLA in April of 2008, and we are happy to be here today at this meeting.

Now I would like to hand it over to Dr. Treanor.

DR. TREANOR: Thank you, Manon. I am John Treanor from the University of Rochester. Our clinical site, which was one of the NIH-sponsored vaccines and treatment evaluation units, was one of the sites that participated in the first study of recombinant hemagglutinin vaccine, followed by a series of studies sponsored by the Division of Microbiology and Infectious Diseases, which were dose ranging studies of both seasonal formulations as well as pandemic

formulations conducted in adults and elderly subjects. Subsequently we were one of the sites that participated in studies that were sponsored directly by PSC, which generated the clinical data that formed the clinical part of the application, which we are going to review today in these slides.

There are four studies which support licensure. PSC01 which was a phase II study, which was dose ranging, in healthy adults between the ages of 18 and 49, and which compared two doses of FluBlok to obtained immunogenicity and safety data as well as preliminary evidence of protective efficacy against naturally acquired influenza.

PSC03, which was conducted in the 2006-2007 influenza season, which looked at non-inferiority of the final formulation of FluBlok in comparison with a licensed trivalent inactivated vaccine in healthy adults 65 years of age and older. PSC04, which was conducted in the 2007-2008 influenza season, which was a field trial to look at the efficacy of the final formulation of FluBlok in a healthy adult population 18 to 49 years of age, and PSC06, which is again a non-inferiority study also conducted in 2007-2008, that compared FluBlok to a licensed inactivated vaccine in a population of healthy adults between 50 and 64 years of age.

PSC04 and PSC01 are comparisons in healthy adults between FluBlok and placebo. They are generating data

relevant to safety as well as to the impact of FluBlok on a surrogate marker, which is recognized as being an excellent correlate of protective efficacy, in this case the hemagglutination inhibition test, and were designed to show that FluBlok induced an antibody response that met or exceeded the 2007 FDA guidance of licensure of an influenza vaccine for seasonal flu.

In addition, PSC04 and 01 generated clinical end point data that document the efficacy of FluBlok in the protection against naturally occurring influenza in comparison to placebo. In contrast, study PSC06 and PSC03, which were conducted in populations for which there is a recommendation for annual vaccination, are studies which compared FluBlok to a licensed inactivated vaccine, and are designed to show that in these populations FluBlok induces an antibody response that meets the criteria in the 2007 guidance. In addition, FluBlok induces a response which is non-inferior to that which is induced by a licensed influenza vaccine.

So we are going to talk about these studies in more detail. In general they have in common that all of these studies are randomized trials which use a modified double blind study design, in which all of the subjects, the study stuff involved in assessing adverse reactions, as well as the laboratory personnel involved in assessing immune responses

and protective efficacy are blinded. Everyone in the study are blinded except for the individuals who administer the vaccine, who are not otherwise involved in the assessment of the outcomes.

These are all multi-center studies which were all conducted in the United States, and they all included healthy adults either ages 18 to 64 in the case of PSC01, 6 and 4, or adults -- I don't know if we would call them elderly nowadays, but people 65 years of age or older, who could have underlying conditions as long as they were medically stable.

For assessment of safety, all four studies utilized a standardized memory aid for collecting solicited AEs for the first seven days after vaccination. In addition, unsolicited AEs were collected through day 28, which was a immunogenicity follow-up visit, and there was a final safety follow-up visit at day 180 in which additional AE information was collected. All adverse events were categorized using standardized definitions in MedDRA coding. For immunogenicity we utilized a standardized and validated hemagglutination inhibition antibody assay which was performed at a single central laboratory, and utilized serologic end point criteria that are suggested in FDA's May 2007 guidance.

The first study that we are going to talk about is

PSC04. This is a pivotal efficacy trial of both the safety as well as the immunogenicity and efficacy as well as lot consistency of the trivalent formulation at 45 micrograms per hemagglutinin, the final selected dose for licensure.

During the 2007-2008 influenza season, there were 4,648 healthy adults ages 18 to 49, randomized to receive a single dose of either FluBlok or saline placebo. The objectives were to assess the safety, lot consistency, efficacy and immunogenicity of FluBlok.

In total, 2,344 subjects received FluBlok, which contained 45 micrograms of each of three hemagglutinins for a total dose of 135 micrograms of hemagglutinin protein. The strain contained in the vaccine included A/Solomon Islands/3/06 which is the H1 component, the A/Wisconsin/67/05 which is the H3 component, and B/Malaysia/2506/04 which is the B component.

I will remind the committee that we are currently faced with a co-circulation of two very distinct lineages of influenza because viruses which are antigenically quite distinct. This particular virus is a representative of the so-called B/Victoria lineage.

An additional 2,304 subjects received saline placebo.

This is an 18 to 49 age group. The mean age in the study was 33, about a 40-60 split between men and women, and

the population was predominantly white, but with a significant representation of both blacks and Latinos as well.

For the end points in the study we defined seroconversion in the following way. For a person who had a detectable level of HAI antibody on day zero at the beginning of the study, seroconversion is defined as a fourfold or greater increase in antibody titer when comparing day 28 to day zero.

For subjects who begin the study with levels of HAI antibody that are below the limit of detection, those individuals must achieve at least a titer of 40 on day 28 to be considered to have had seroconversion. I will remind you that the May 2007 seasonal guidance suggests that for adults less than 65 years of age the vaccine should induce seroconversion at a rate so that the lower bound of the two-sided 95 percent confidence interval around the proportion of individuals responding should meet or exceed 40 percent.

This slide shows the percentage of individuals in the study who had a seroconversion, as defined previously, for each of the three components of the vaccine, along with the 95 percent confidence intervals around the estimate of the proportion with seroconversion. The red line represents that 40 percent guidance that the lower bound should exceed. So you can see here that for the H1, the H3 as well as the B

component that the lower bound of the 95 percent confidence interval clearly exceeds that 40 percent guidance.

In the study, seroprotection is defined as the achievement of a post vaccination HI titre of 40 or greater. The 2007 guidance suggests that a vaccine should include seroprotection at a proportion such that the lower bound of the two-sided 95 percent confidence interval would meet or exceed 70 percent.

This is a similar graph, which now shows in blue the proportion of subjects in the vaccine group who achieved the titer of one to 40 or greater against each of the three components of the vaccine with the 95 percent confidence interval, as well as the 70 percent boundary suggested in the 2007 guidance document. We can see that for all three components, the lower bound of the 95 percent confidence interval clearly exceeds 70 percent.

This slide shows the GMTs against each of the three vaccine components on day zero and on day 28 in vaccine recipients. The numerical value at the bottom of the bar chart shows the actual GMT, and you can see that for each of the three components there is a substantial increase in HAI antibody comparing day 28 with day zero.

In PSO04 the subjects in the study were followed after day 28 for the development of influenza-like illness. In this study the subjects were called each week. They also

had a memory card in which they were to record any respiratory symptoms. Individuals who met the respiratory symptom score of two or greater were to return to the study site where a nasal and throat swab were obtained for viral culture in rhesus monkey kidney cells.

Those isolates in rhesus monkey kidney cells that grew were then further classified antigenically by reciprocal HAI using post infection antisera, which is the standard method for characterizing the antigenic relatedness of influenza virus isolates.

So there were several potential isolates of this study. An individual could develop a respiratory illness. Among those individuals who developed a respiratory illness, some of them would meet the CDC influenza-like illness definition which requires a fever as well as the presence of either cough or sore throat. Among those individuals who have illness and are cultured, some of them would be culture positive and some would be culture negative. Then among the individuals who are culture positive, some of them would have a virus isolated that was antigenically related to a vaccine component, and some would have a virus isolated that would be determined to be antigenically drifted from the vaccine. So those are all potential outcomes of this study.

The primary efficacy end point in PSC04 is the development of an illness meeting that CDC ILI case

definition with a positive nasal throat culture for an influenza virus strain that has shown by reciprocal HAI to antigenically match one of the strains contained within the vaccine.

The sample size chosen for the study 4,318 randomized one to one. That is based on an assumption of a vaccine efficacy of 70 percent, and an attack rate in the placebo group of three percent, which would give the study approximately 80 percent power at alpha equal point .05 to achieve the goal of demonstrating efficacy with a lower bound of 40 percent, assuming a five percent attrition rate in each group.

Unfortunately this influenza season was characterized by suboptimal match between the vaccine strains and the circulating strains for all three of the components. As you are all very well aware, this is an ongoing issue with influenza vaccines generally. According to the CDC influenza activity website, 77 percent, 33 percent and 98 percent respectively of the H3, H1 and B isolates during the 2007-2008 season in the United States were antigenically dissimilar from the 2007-2008 vaccine strains. You know that this varies geographically. Another issue with vaccines is that there are slight differences from place to place in how that plays itself out.

But in particular, the predominant circulating B

strain in that season was of a different lineage, the so-called B/Yamagata, than the one that was represented in the vaccine, which was a B/Victoria lineage virus.

If we look at clinical efficacy against the primary end point, that again is CDC ILI with a virus isolated that is antigenically similar to one in the vaccine, there were 273 subjects in the FluBlok group who had an illness and a nasal throat swab with pain, 309 subjects in the placebo group. From those subjects, 64 individuals had a positive culture in the FluBlok block and 114 had a positive culture in the placebo group.

The majority of these influenza viruses did not meet the definition of an antigenic match to one of the vaccine strains. So there were only eight viruses that were an antigenic match. All of these were H3 viruses that matched the A/Wisconsin. You can see the distribution. Two of these were isolated from vaccine recipients, six were isolated from placebo recipients. Among those eight people, five of them actually met the CDC ILI case definition, so that at the end of the day there was only one subject with a culture positive CDC ILI with an antigenic match to the vaccine in the vaccine group and four individuals in the placebo group. This gives a protective efficacy of 75.4 percent. Because of the very small numbers, obviously this is not statistically significant, with very wide confidence

intervals.

This is a characterization of the viruses that were isolated in the study. Again, 64 viruses isolated in the FluBlok group and 114 isolated in the placebo group. Among the B viruses essentially all of them were representative of the B/Florida 2006 virus, which is a different lineage from the vaccine. You can see the distribution. There are less of those in the vaccine group than there are in the placebo group. There was one virus that could not be identified further in terms of its antigenic characterization.

Among the small number of H1N1 viruses that were isolated in the study, all of them were similar to A/Brisbane, which is a drift variant that was included in the vaccine in the subsequent season.

Among the H3 viruses it is a bit more complicated. As I mentioned earlier, eight of these viruses represented the A/Wisconsin vaccine strain. There were an additional large number of viruses that could be definitively identified as resembling A/Brisbane 2007 which was subsequently chosen for the vaccine in the next year.

There were an additional group of viruses in which the antigenic relatedness could not be determined. You may know if you do this test that there are low reactors and viruses that don't seem to react with either of the typing sera. There were additionally a small number of viruses that

were positive in cell culture, but then could not be re-isolated and therefore could not be further typed as a specific subtype of A.

There were two pre-specified exploratory end points for PSC04. One was the development of an illness meeting the CDC ILI definition associated with a positive culture for any influenza virus strain regardless of match. The other one was the development of a CDC ILI regardless of culture result, so somewhat of an effectiveness end point against the global illness resembling influenza clinically.

This slide shows that there were 44 subjects who had a culture positive CDC ILI illness regardless of antigenic match in the vaccine group of 1.9 percent and 78 individuals in the placebo group or 3.4 percent. This results in a protective efficacy of 44.6 percent with confidence limits from 19 to 63 percent. This is highly statistically significant, and demonstrates that for that pre-specified secondary end point, FluBlok demonstrated significant protective efficacy against CDC ILI associated with influenza.

If you look at more of an effectiveness end point of individuals who experienced any kind of CDC ILI regardless of culture, there also is a positive protective effect with 5.4 percent of FluBlok recipients reporting that kind of illness and seven percent of placebo recipients, which is a

protective efficacy of 22.9 percent. Again, this is statistically significant with 95 percent confidence intervals that do not overlap zero.

I will just mention parenthetically, you may remember, Christine Nichols did a similar study with inactivated vaccine in the '90s in which she demonstrated 25 percent effectiveness in prevention of CDC ILI in a population of healthy adults with standard inactivated influenza vaccine.

Exploratory end points to try and look individually at effectiveness against influenza A or B. The top series of lines has the data that you already saw. If you break this down into influenza A or influenza B among individuals with CDC ILI in whom any influenza A was isolated, you can see 1.1 percent of FluBlok recipients and 2.4 percent of placebo recipients for a protective efficacy of 54.4 percent against CDC ILI due to any influenza A strain. This is mostly mismatched A3 and 2, among any person who has a culture positive illness regardless of whether they meet that case definition of CDC ILI. This is mostly individuals who had an illness without a documented fever. You can see 49 percent efficacy in the prevention of culture documented illness. Both of these numbers are statistically significant with 95 percent confidence intervals that did not overlap zero.

For influenza B, as expected vaccine efficacy is

not as good for influenza B because of the very large antigenic distance between the two lineages of B. Looking at individuals with culture positive CDC ILI, you can see a 23.1 percent protective efficacy. This does not meet statistical significance with 95 percent confidence intervals that overlap zero. Considering all culture positive subjects, the protective efficacy is slightly higher at 37.2 percent, but does not quite meet statistical significance with a lower bound of -8.9.

Just to put this in context, observers of the influenza C realized that with influenza vaccine, every year represents a different trial of a new vaccine against a new influenza strain. This is a recognized issue and has been since the 1950s. So estimates of influenza vaccine effectiveness vary from year to year.

These are some recent estimates, admittedly generated using a variety of study designs. But you can see that they range from a low of ten percent in the Belongia study with a poor match, 22 percent in a recent year in a randomized control trial to somewhat higher levels in case control studies, up to 52 percent, and most recently 68 percent were TIV in a comparison study done at the University of Michigan at a clinical site where there was relatively less impact of a mismatch of B because there were relatively few B isolates.

So all in all, with PSC04, protective efficacy data falls right in the middle of the range of recent data looking at efficacy or effectiveness of influenza vaccines.

The vaccine was very well tolerated in this population of otherwise healthy adults. These graphs show the proportion of individuals reported solicited adverse events in the seven days post vaccination. Most of these events are reported within a few days of vaccine, and they are generally mild. As expected, the proportion of individuals with pain at the site of immunization is higher in those receiving FluBlok than it is in placebo recipients. Other solicited adverse events occur at a similar rate between vaccine and placebo recipients.

Systemic adverse events occur at a rate between vaccine and placebo recipients. This is a very consistent finding in studies of inactivated influenza vaccines generally, which typically don't show differences between vaccine and placebo in the rate of systemic adverse events in the week following vaccination.

Unsolicited AEs were reported in 17 percent of FluBlok recipients and 17 percent of placebo recipients. Headache and upper respiratory tract symptoms were the most commonly reported unsolicited AEs. There was no notable imbalance between the study groups for any specific unsolicited AE.

There was one case of Bell's palsy reported in the FluBlok group. This is in the briefing document. This is an individual who had a prior history of Bell's palsy. He had the onset of symptoms within one hour of vaccination. This was classified by the site investigator as not related.

There were 20 pregnancies in the FluBlok group, and there were no adverse outcomes related to vaccine in these 20 pregnancies. Nine subjects withdrew as a consequence of AEs, five in the FluBlok group and four in the placebo group, and seven of these withdrawals were due to pregnancy.

There were 85 serious adverse events reported in 64 subjects for a rate of 1.4 percent, equally distributed between FluBlok and placebo recipients with 41 events reported in 30 FluBlok recipients and 44 in 34 placebo recipients. Eighty-four out of 85 SAEs were considered unrelated, including the two deaths, a pulmonary embolism in the FluBlok group and a motor vehicle accident in the placebo group.

There was one possibly related serious adverse event in a FluBlok recipient. This was in a 47-year-old male who was hospitalized 11 days post vaccination because of a pleural effusion. A very substantial workup did not reveal a cause. He was discharged 13 days after his admission and fully recovered.

PSC01 is a very similar but much smaller study that

was done earlier to evaluate the immunogenicity and safety and also protective efficacy of the trivalent recombinant baculovirus expressed hemagglutinin. This study also contained a dose ranging element that led to selection of 45 micrograms as the final dose.

I'm not going to go into this in detail because the study was published a number of years ago. This is a phase II study that Dr. Pandey discussed earlier, conducted in 458 healthy adults during the 2004-2005 influenza season, with the objectives to evaluate the dose related safety and immunogenicity of FluBlok. But in addition these participants were also followed during the influenza season to evaluate protective efficacy.

They were randomized to receive a single dose of recombinant hemagglutinin at either a total of 135 micrograms, which is 45 micrograms per component, the same dose which is being submitted for licensure, or they received a 75 microgram dose which contained only 15 micrograms of the H1 and the B component, and contained 45 micrograms of the H3 component.

So the important thing here is that with respect to the H3 component, both levels were the same. The components in this study were A/New Caledonia as the H1 component, A/Wyoming as the H3 component, and B/Jiangsu, which is a B/Yamagata lineage virus as a B component. 153 subjects

received 100 doses of vaccine, 151 low dose vaccine and 154 subjects received saline placebo.

The age group is very similar to the last study, with a male-female ratio of about 40-60, a mean age of 31, and in this study a predominantly Caucasian population.

These are the same definitions of seroconversion as we talked about earlier, a fourfold or greater increase in the antibody in individuals with detectable antibody at the beginning of the study and achieving a titer of 40 or greater in individuals who are below the limit of detection.

However, when this study was done, it was initiated before the FDA guidance document had been published. So as those of you who are aficionados of the HAI test know, there are two schools of thought about how it should be done. Some people start at a one to four dilution, some people start at a one to ten dilution.

If you start at a one to four dilution, which is the dilution that was used in this study, it becomes difficult to use one to 40 as a cutoff because that is not one of the dilutions that you would have. You would have one to four, eight, 32 and 64. So this makes the analysis of the study a little iffy, and I'll show you what I mean by that.

We are going to present data for individuals whose titer either exceeds 64 which is over one to 40, or 32, which is closer to one to 40 but slightly under that. That is an

artifact of the way the dilutions were done.

Here is the proportion of individuals who achieved that higher titer of 64 or greater, again presented in the same way, with the black bar showing the 95 percent confidence interval and the red line showing the FDA guidance. With respect to H3, both dose groups have the same proportion as expected because they have the same H3 content, and they both exceed the FDA guidance.

With respect to H1 there is a dose response with a better response to 45 micrograms than 15 micrograms. At the 45 microgram dose which is the dose that is being suggested for licensure, also exceeds the guidance. Similarly, with B there is a clear dose response effect with a better response of 45 micrograms shown in dark blue, and at that dose the B component also exceeds the FDA guidance.

In terms of seroconversion, if we look at a one to 32, this is basically the same data, but now shows that the H1 and the B component would be very close to meeting the FDA guidance even if you looked at the 15 mechanism dose.

For seroprotection, the issue is, the guidance document defines seroprotection at one to 40, so we have an option of looking at one to 32 or one to 64.

This shows the data if we select achieving a titer of one to 64 as the end point. You can see a dose response relationship between the 15 and 45 microgram doses of H1, and

the H3 component is very immunogenic if you are looking at those achieving a titer one to 64 or higher.

For the H1 and the H3 component, the 45 microgram dose exceeds the guidance for the proportion with seroprotection. For the B component, only 65 percent of those individuals achieve the titer one to 64 which does not meet that guidance. But if we use the one to 32 titer cutoff, all three components meet the 70 percent lower confidence interval guidance for seroprotection.

This shows the GMTs of antibody in PSC01. You can see on day 28 that there is a dose response in terms of GMT for the H1 and the B component but not the H3 component because the H3 has identical levels of antigen in both dose groups.

This is a small study, so there are a relatively small number of cases of influenza. These are defined in exactly the same way as I mentioned for PSC04. There were 39 subjects in the 75 microgram group and 34 subjects in the 135 microgram group with an illness, 43 subjects in the placebo group. Most of these isolates were H3N2 viruses, and you can see the relatively small number of influenza isolates in the study.

Overall, if you look at the two FluBlok groups combined, since most of the isolates are H3 viruses, 1.7 percent of FluBlok recipients had a culture positive illness

compared to 5.2 percent of placebo recipients.

If we simply look at those individuals with culture positive CDC ILI, there is a protective efficacy if you combine the two FluBlok groups together of 85.5 percent, with a confidence interval of 23.7 to 98.5. This is statistically significant. If you look at individuals with a CDC ILI regardless of whether they were culture positive or not, there is a suggestion of effectiveness against that less specific end point of 41.5 percent with confidence intervals that overlap zero. The P value for that comparison is 0.9.

If we look specifically at the H3N2, you can see a protective efficacy of 79.2 and for H3N2, regardless of whether or not the CDC case definition was met, the protective efficacy was 68.2. Because of the small numbers of subjects these did not meet statistical significance.

Vaccine was also well tolerated in this study. Pain was the only side effect or solicited adverse event that was substantially increased over placebo. Swelling was slightly increased over placebo as well.

For systemic adverse events, the rate of solicited systemic adverse events is similar in the vaccine and the placebo group, consistent with many other studies of inactivated influenza vaccine.

Unsolicited adverse events were reported by 35 percent FluBlok recipients and 42 percent of placebo

recipients. Headache and upper respiratory tract symptoms were the most commonly reported unsolicited adverse events, with no imbalances between study groups.

SEAs; there was a person who had a seizure secondary to hypoglycemia on day 26 following vaccine in the FluBlok group. There was an individual who was diagnosed with lobular carcinoma in situ on day 55. Both of these AEs were considered unrelated, and there were no study withdrawals due to adverse events.

We are going to switch gears and talk about studies that are designed to FluBlok with a licensed inactivated vaccine in populations for which there is an indication for annual vaccination.

PSC06 is a study which compares FluBlok to a licensed comparitor which happens to be Fluzone in otherwise healthy adults aged 50 to 64. In this study there were 602 healthy medically stable adults that could have chronic pre-existing conditions as long as they were medically stable. Age 50 to 64 years, who were assigned to receive a single dose of either FluBlok at the commercial formulation of 45 micrograms per dose or a commercially available trivalent influenza vaccine, which happens to be Fluzone. This study was conducted in 2007-2008. The objectives were to evaluate safety and reactogenicity and to compare immunogenicity again using that surrogate marker that is recognized as an

excellent correlate of protective efficacy.

300 subjects received FluBlok, 302 subjects received Fluzone. The components of FluBlok and Fluzone were the same, including Solomon Islands as the H1 component, Wisconsin as the H3 component, and B/Malaysia as the B component, which happens to be in that year a member of the Victoria lineage.

The mean age was 56, more or less in the middle of that age group, about a 40-60 split male to female, in a predominantly white population with some Hispanics and African-American and Asian participants.

To reiterate again seroconversion, this time we are back to using one to ten as the starting dilution, so seroconversion is defined as a fourfold or greater increase in antibody for those with antibody at the beginning of the study, and the achievement of a titer of 40 or greater in those who start below the limit of detection. And for individuals under 65, we want the lower limit of that 95 percent confidence interval to meet or exceed 40.

This shows the proportion of individuals who meet that definition of seroconversion against each of the three components for those who receive FluBlok or those who receive Fluzone along with the 95 percent confidence intervals shown in black, and the 40 percent limit suggested in the guidance document shown in red.

For both H1 and H3 viruses, FluBlok achieves a 40 percent or greater seroconversion guidance. Neither FluBlok nor Fluzone achieved the 40 percent or greater guidance for the B/Malaysia component, and in addition FluBlok did not quite make the guidance for the H3 component.

This slide which is also in your briefing document gives the specific numbers. Where they are colored in green, this indicates that the vaccine met or exceed the FDA guidance, in pink are those that did not. For FluBlok with regard to seroconversion, the guidance was exceeded for the Solomon Islands H1 and the Wisconsin H3, but not for Malaysia. For Fluzone it was exceeded for Solomon Islands H1 but not for the H2 or B component. These are very, very close, the ones that failed to meeting the 40 percent, with lower limits of 35 to 38 percent.

With regard to seroprotection, the definition of seroprotection is achievement of a titer of 40 or greater. We would like to see the lower limit of the two-sided 95 percent confidence interval exceed 70 for this population of adults less than 65.

This shows the proportion of individuals on day 28 considered seroprotected in the group that received FluBlok and the group that received Fluzone for each of the three components. In this case in the dark blue FluBlok has achieved the FDA criteria for all three components, the H1

Solomon Islands, the H3 Wisconsin, as well as the B/Malaysia in which 93 percent of subjects achieved seroprotection.

For Fluzone the same is true except for a close result with the H3N2 component. This is shown in more detail here. The green bars are ones where the guidance was exceeded, the pink bars are the ones in which it was not, and in the case of Fluzone it is 69.9 percent as opposed to 70 percent, so a relatively tiny difference there.

So both vaccines exceed the guidance here for all three components.

This looks at a comparison of the pre and post GMTs for all three antigens between Fluzone and FluBlok, FluBlok shown in dark blue, Fluzone shown in gray, with a 95 percent confidence interval. This is a logarithmic scale, so to help you read this, the actual values are numerically displayed on the bottom. Fluzone and FluBlok elicit very comparable titers, with slightly higher titers against the H1 and the H3 components in the FluBlok group, and a very slightly higher titer against B in the Fluzone group.

We also have non-inferiority criteria which have been suggested by FDA for comparison of an experimental vaccine with a licensed comparitor vaccine. In this case, the FDA suggests that the upper bound of the two-sided 95 percent confidence interval on the ratio of GMTs, comparing the GMT of the licensed vaccine to the GMT of a new vaccine

should not exceed 1.5.

This is hard to imagine intuitively. The ratio is between a licensed vaccine and the experimental vaccine. If the ratio is less than one, that means that the experimental vaccine resulted in a higher titer. If the ratio is more than one, that means that the experimental vaccine resulted in a lower titer. The idea here is that we would not want to see a situation where a licensed vaccine elicited a 50 percent higher titer than a new vaccine. So that is the boundaries of that guidance.

The difference in seroconversion rates, the guidance says that that 95 percent confidence interval on that difference should not exceed ten percent, because the comparison is between licensed and experimental vaccine and negative difference mensa that the experimental vaccine performed better, and a positive difference means that the licensed vaccine performed better.

These are the comparisons for the three components in PSC06. For most comparisons they are either less than one or negative numbers, suggesting that FluBlok performed better than Fluzone. In all cases the FDA guidance for non-inferiority based on serologic criteria are met for FluBlok in PSC06.

This shows local solicited adverse events in this study. The most commonly solicited local event is pain at

the site of administration. This is mostly mild and is not significantly different between FluBlok and Fluzone.

Systemic adverse events are generally mild, occur at a low rate, and again occur at a similar rate between FluBlok and Fluzone with one of the comparisons, Fluzone, has a slightly higher rate of fatigue than FluBlok, but generally the comparisons are very similar between the two vaccines.

Unsolicited AEs were reported in 14 percent of FluBlok recipients and 17 percent of Fluzone recipients. For FluBlok, the imbalance was an erythema at the injection site at the immediate post vaccination period, which occurred in two percent of recipients, and cough in two percent. For Fluzone, sore throat was reported in three placebo and rhinorrhea in two percent as the more commonly reported with Fluzone.

There were many imbalances in both directions, none of which were felt to be clinically concerning. Twenty FluBlok recipients or seven percent and 22 Fluzone recipients, also seven percent, and AEs that were classified as related or possibly related to study vaccine. Most of these were signs and symptoms of URI. I will say parenthetically that for reasons that escape me, investigators almost always attribute URI symptoms to the vaccine. I don't really know why, but that is very typical.

None of the subjects withdraw as a consequence of

adverse events.

There were four SAEs reported in four subjects, two in the Fluzone group, two in the FluBlok group. In the FluBlok group, one individual fainted after vaccination, and that was felt to be related, and one individual developed acute pancreatitis about day 28 after vaccination, which was considered unrelated. In the Fluzone group an individual has prostate cancer, another person had a stroke, both of which were considered unrelated, and there were no deaths reported in either group.

The final study I will talk about is PSC03. This is a similarly designed comparison of Fluzone and FluBlok in a population of individuals 65 and older. This is in press in *Vaccine*; it should come out soon, by Wendy Keitel.

It is a phase II-III trial. It was conducted in the 2006-2007 flu season for medically stable adults. These individuals could have chronic conditions. They had to be medically stable. It evaluates the commercial formulation of FluBlok with 45 micrograms of each component, and Fluzone is a licensed comparison, and the objectives again are to evaluate safety, immunogenicity and protective efficacy.

436 subjects received FluBlok, containing New Caledonia/20/99 as the H1 component, A/Wisconsin H3N2, and B/Ohio as a representative of the B component; that is a member of the B/Victoria lineage. 433 subjects received

Fluzone as a single dose that contained 15 micrograms of each of the three hemagglutinins for a total of 45 micrograms.

As it turns out, after the study was designed, during the process of making the vaccine the egg manufacturers decided to switch from B/Ohio to B/Malaysia because of difficulties in generating an appropriate seed virus for the B/Ohio. This is one of the issues that does come up with using the egg systems to create vaccine. So for the comparison of B, we were left with a comparison that does not directly compare the same antigen in both groups.

This is a group over 65. The mean age was 73. Male and female ratio is closer to one to one here, 48-52 percent, and this is predominantly a white and Caucasian group.

We used the same definitions of seroconversion here, but bear in mind that the guidance document for the elderly is a little bit more lenient, and suggests that the lower bound of the two-sided 95 percent confidence interval for that seroconversion rate should meet or exceed 30 percent rather than 40 percent for older adults.

This in a very similar way shows the proportion of individuals who meet that definition of seroconversion among all the subjects, and then among those subjects who are 75 healthy adults or greater. That is slightly less than half the subjects. Remember, the mean age was 73 in the study.

If you look at the group as a whole, FluBlok shown in dark blue meets the guidance for the H1 and the H3 component. Fluzone meets the guidance for the H3 and the B. Each of the vaccines failed one of the comparisons. The B component again is complicated by the fact that it is somewhat of an apples and oranges comparison, in that we are testing Ohio for FluBlok and Malaysia for Fluzone. Those differences are maintained if you look exclusively at this population of individuals 75 and older, although the confidence intervals tend to be wider because the numbers of subjects are smaller. FluBlok meets or exceeds the guidance for the H1 component and the H3 component, if you look at the relatively older population of elderly subjects.

This table shows the specific numbers, including the lower bounds of the confidence intervals. A green box means that with respect to that comparison, the vaccine met or exceeded the guidance for H1 in terms of seroconversion. The guidance is met for FluBlok both in all subjects and subjects over 75. For Wisconsin, both FluBlok and Fluzone meet the criteria both in all subjects and those subjects 75 and older. For B FluBlok did not quite meet the guidance for either, and Fluzone met it for the population as a whole, but not for those over 75.

Seroprotection defined in the same way, as achieving a titer of 40 or greater. In this case, for

individuals 65 or older we are looking for a two-sided confidence interval that meets or exceeds 60 percent.

This shows the proportion of individuals in each group who achieve a titer of 40 or greater on day 28 post vaccine with the 95 percent confidence intervals, and you can see that both Fluzone and FluBlok clearly meet that guidance with respect to the H1, the H3 and the B component.

We also looked as an exploratory analysis at the relative antibody at the end of the influenza season to see how much of a follow-off there might be in the proportion of individuals who had that titer of one to 40 or greater, and whether there were significant differences between the two groups with respect to the duration of protective antibody. There are not substantial differences between FluBlok and Fluzone in the resistance of antibody, with most subjects in both groups maintaining titer of 40 or greater throughout the flu season.

This is a comparison of the geometric mean titers between the two groups on day zero and day 28. There is a difference in the titers predominantly of the H3 component between the two groups, and that the B component is slightly higher in the Fluzone group than the FluBlok group, although the 95 percent confidence intervals overlap in that comparison.

In terms of those non-inferiority comparisons that

we talked about earlier, that the ratio would not exceed 1.5 and the difference would not exceed ten percent, with regard to non-inferiority comparisons for geometric mean titer, FluBlok in comparison to Fluzone meets that guidance for both the H1 and the H3 component. Parenthetically, 95 percent confidence intervals do not cross one, so the titers are higher in those who receive FluBlok. It also meets the guidance for the B component. For differences in seroconversion rate, FluBlok meets the guidance for both the H1 and the H3 component, but does not quite meet the guidance for the B component, partially because of those differences in comparisons.

Local adverse events were reported in frequently in these elderly recipients. A characteristic of the elderly is that they don't complain as much as young people do about side effects. There are relatively low rates of solicited local adverse events which are similar between the two groups. Systemic adverse events also occurred rarely, were generally mild, and were quite similar in the Fluzone and FluBlok recipients.

Unsolicited AEs were reported in approximately 20 percent of both groups. Injection site reactions, headache, URI symptoms were most commonly reported. There were some imbalances between the treatment groups, in particular for FluBlok erythema at the injection site was reported more

frequently in those who received FluBlok than Fluzone, as well as swelling and bruising, and those two latter differences are not statistically significant.

These injection site reactions were detected by the investigator. In this particular study, the issue was instructed to measure the size of the erythema around the injection site. These are not things that were noticed by the subject, so they are not actually symptomatic. The subjects would probably not have reported this unless it was being measured. All resolved within seven days, and none of the subjects withdrew as a consequence of adverse events.

This is an older population. There were 70 serious adverse events reported in 70 subjects; 36 were in FluBlok recipients, 34 in Fluzone recipients. There were two deaths in each study group, all four of which were considered unrelated. Two in the FluBlok block, a person with a perforated viscus and a hemorrhagic stroke, two in the Fluzone group, an individual with a heart attack and a diabetic who suffered a sudden cardiac arrest. There were no demonstrable imbalances in serious adverse events between the two study groups, and all serious adverse events in both groups were classified by the site investigator as unrelated.

I am going to just go over this very briefly across all studies, looking at these criteria one more time.

This is seroconversion for H1N1 across all the

studies. The red line is different in the younger people than the older people. Looking again at FluBlok and placebo in four and one, and Fluzone and FluBlok in six and three, and you can see that with respect to H1, FluBlok exceeds the guidance for all studies, here in blue with the black bar showing the 95 percent confidence intervals.

Seroconversion to H3. The blue dots are FluBlok, yellow is placebo, gray is Fluzone, 95 percent confidence interval shown in black. With respect to H3, FluBlok meets or exceeds the guidance for seroconversion across all four studies.

For B, FluBlok is shown -- it is supposed to be blue, but it looks kind of gray on my screen, but it is the one on the left, with a 95 percent confidence interval. For the population from 1849 FluBlok meets or exceeds the guidance for B. For PSC06, neither FluBlok nor Fluzone met the guidance, and for PSC03 FluBlok did not meet the guidance, whereas Fluzone did, complicated by that different comparison.

For seroprotection, same presentation. FluBlok meets the guidance across all studies. For seroprotection for H3, FluBlok meets the guidance across all studies. For seroprotection against B, FluBlok meets the guidance across all studies except for PSC01.

For the non-inferiority differences for all three

components where this was compared for difference in GMT ratio, FluBlok meets the guidance for non-inferiority in comparison to Fluzone in both younger as well as older adults for all three components.

For difference in seroconversion rates, FluBlok meets the guidance for the H1 and the H3 component in PSC06 and 3, and meets the guidance for the B component in PSC06, but not for PSC03 where the difference exceeded that ten boundary.

An overview then of solicited adverse events. This gives the rates in all four studies in comparison to the comparitor group for 01 and 04 in comparison to placebo, 06 and 03 in comparison to Fluzone. It also gives you an indication of the number of individuals who were involved in these studies. For comparisons with Fluzone, the rates are very similar. For comparisons with placebo, the one thing that stands out as being more common is pain at the site of injection, as expected with an inactivated influenza vaccine.

Looking at solicited systemic adverse events, in comparison to placebo the rates are very similar. In comparison to Fluzone very similar rates of solicited adverse events.

With that, I will turn it over to Manon to give an overview of the summary.

DR. COX: Thank you, Dr. Treanor, that was

excellent. I will now in the next eight slides present the data once again, but now in great summary.

As John explained, in green in the various slides you will see where we meet the criteria as per FDA guidance and in red where criteria are not met as per FDA guidance.

As we will see here, we have in this slide summarized PSC01, PSC04 for FluBlok and then PSC06 and 03 we report both FluBlok and Fluzone. In PSC03 we failed to meet one of the six criteria for Fluzone in PSC04. We passed all criteria in PSC06. One of the criteria, seroconversion for B, was -- one of the criteria was missed for seroconversion of the B strain, where Fluzone missed two of the six criteria.

Then PSC03, where as John pointed out we had different components for the B strain, we missed the seroconversion criteria and FluBlok missed the seroconversion criteria for the H3 strain, whereas we miss it with FluBlok for the B component.

As far as non-inferiority comparisons are concerned, in green you see in 11 of the 12 instances FluBlok meets the non-inferiority criteria, whereas in one of the 12 comparisons does not meet the criteria.

Where we have indicated, FluBlok greater than Fluzone we have a result where FluBlok is significantly higher than the Fluzone comparitor.

This summarizes those two slides in words. Seroconversion and seroprotection in studies PSC03 and 06, when we combine the results, FluBlok meets ten out of 12 end points, where Fluzone meets nine out of 12 end points. We say here or eight, but if we round up the numbers we end up with nine out of 12 end points. PSC01, 04, 03, 06 combined, we meet 21 out of the 24 end points.

If we look again at non-inferiority as compared to Fluzone, we see that FluBlok was non-inferior to Fluzone in 11 out of the 12 comparisons that were presented.

The summary of the efficacy is shown here. As John indicated, 2007-2008 in our hands was a study where 95 percent of the viruses that we isolated represented a drift variant from what was included in the vaccine. Still when we look at the very specific end points, we see an efficacy of 75.4 percent against cell culture CDC ILI positives, but the confidence interval is very wide due to the low number of cases that we have, only five in this. Then if we look for matched strains not meeting the CDC ILI fever criteria, we are looking at a 67 percent efficacy, and confidence interval very wide.

What is important obviously for influenza is that we can never predict what the circulating strains will be in the year of the outbreak, does the vaccine also work when there is a mismatch in the vaccine. So what we show here is

the efficacy results against all strains. Despite that suboptimal match, we see an efficacy of 44 percent with a confidence interval of 18.8 to 62.6 percent. If we split that out into type A and type B, which you want to do because the type B virus isolates all belong to the different lineage, we see an efficacy against type A influenza of 54.4 percent with a confidence interval of 26.1 to 72.5, and for type B, 23.1 percent with a confidence interval that overlaps zero.

This is not significant.

Also, PSC01 was a placebo controlled trial. In this study we showed with the higher dose 100 percent efficacy, although if you combine the results of both the lower dose vaccine with the higher dose, that efficacy goes down to somewhere in the 80s. Also, in this season all the viruses that we isolated would be characterized as antigenically different.

Then in PSC03 and 06, while we looked for cases, the number of cases was too small to draw any meaningful conclusions.

A summary of the safety. The commercial formulation of FluBlok was evaluated in a total of 3,233 adults in four randomized control studies. All these people received the commercial formulation. If we would add up all the people that received any dose or any composition of

FluBlok, we would end up with a database that would be greater than 5,000, but let's focus here on who received the commercial formulation. 2,496 adults of 18 to 49 received the commercial formulation, 300 adults aged 50 to 64 and 436 adults older than 65.

What we have shown is an excellent tolerability and safety profile with adverse events rates generally similar to the active comparitor, which was Fluzone in both studies.

There was one treatment related serious adverse event which was a syncope, and one possibly related serious adverse event reported.

We are still in discussions with the FDA what the requirements of postmarketing surveillance will be. We have proposed to conduct a large observational study where we are going to look for signals in a very large population. We have proposed to examine doses of FluBlok over multiple years to the agency. But since we have not received feedback or had the opportunity to discuss that, we do not want to go into greater detail at this moment.

In conclusion, FluBlok addresses a medical need as it can be used in egg-allergic subjects. The manufacturing process does not use eggs. This would be the first cell culture based influenza vaccine that would be available if licensed. The production cycle is short. In principle, once we are in manufacturing, every five days you can complete a

production batch. As I have shown during the introduction, within a month after receipt or within two months after receipt of virus, one could be in commercial manufacturing.

The higher antigen content offers potential benefits to those at greater risk for influenza. FluBlok is expected to provide a significant public health benefit.

That is where I would like to end this presentation.

DR. STAPLETON: Thank you, Dr. Cox. Are there questions and discussion from the committee at this point?

DR. GELLIN: On your summary, everyone focused on time line. So give us an example. If a virus were to emerge, when would vaccine be available? What is a realistic time line from the time a new virus might emerge to when the vaccine could be available to give to people?

DR. COX: It might be good to go back to the slide that shows the time line. To answer your question, Dr. Gellin, when we will see the virus, when we are totally not aware of what the virus will be, for example as was the case with the novel H1, it basically takes us about three to four weeks to generate a recombinant baculovirus stock that can be produced in production.

So in other words, within five weeks you would be cranking out your first batches of vaccine, but then there is obviously the product release testing that needs to occur.

That today still takes 30 days because of the mycoplasma steroplasma test and various other tests that need to be conducted.

If you on the other hand have -- and this is what I would envision in most seasons -- if you have your recombinant baculovirus working stocks already frozen down, you will reduce that time line from 30 days to like maybe one or two weeks, because then it is a matter of thawing your frozen virus stocks and starting manufacturing right away.

DR. GELLIN: I guess I would like a clear answer to when vaccine would be available to provide to an individual.

DR. COX: I would say that a very realistic time line there would be 75 days.

DR. GELLIN: Thank you.

DR. STAPLETON: Somewhat related to that, there is no much variation in your ability to produce based on the sequence. So do you make multiple stock plasmids, or do you use a single? There is a difference.

DR. COX: What we in principle do is, we take a look at the sequence that CDC publishes for their isolates and we indeed select many, many variants to find that particular -- as you can imagine, when you receive a mix or a virus from CDC, this will contain many different hemagglutinin gene sequences. So we do screen in general about ten different isolates and then pick the one which

matches the CDC reference sequence. But at some point in some instances, CDC's reference sequence might not be totally available, and for that reason we will continue in the future to select a few more components. We are working with CDC to come closer to a good antigenic variant.

One of the advantages of this system is that you can make a matching hemagglutinin to the hemagglutinin that is actually circulating in the field. We are trying to do that as well as we can. But at the same time we also need to stick with what was sequenced, so that everybody understands that we are making what was recommended by the VRBPAC committee.

DR. STAPLETON: On the technical side, is there much difference between related viruses and expression, or are they all fairly similar?

DR. COX: In principle they are fairly similar. There are differences between the H1s and the H3s and the Bs, but that relates basically more to the downstream process, the purification of the antigen.

DR. LEVANDOWSKI: I have got a question to follow up on what Bruce Gellin was asking. In terms of the time line, what impact does the availability of those reagents have on your capabilities to deliver product? If y0u are using different strains, let's say, what is going to be done to accommodate those time lines?

DR. COX: On one level our product is a purified protein vaccine, so we do have the ability to use different analytics to determine what the antigen content is. At the same time, we are also working on developing alternative methods that will look for immunologic parameters as well.

At this moment in time, our seasonal product release depends on the availability of SYD reagents from the agency. I think that was a choice we made to standardize our vaccine, unlike the vaccines that are currently on the market. Does that answer your question?

DR. DEBOLD: I have three quick questions as a public representative. You said that the FluBlok manufacturing process does not use eggs, but yet on slide five it talked about infecting chicken embryos. Can you please clarify that?

DR. COX: I'm sorry. What I was trying to do on slide five is give you a very quick overview of what the current licensed vaccine manufacturing process looks like.

DR. DEBOLD: I see, great. Thanks. Then on slide 83, the titers that are listed there on day zero, are these the titers that somehow has prior to being vaccinated? So would we interpret some of these as being protective?

DR. TREANOR: These titers are the titer of antibody that they have when they come into the study.

DR. COX: She said 83, slide 83.

DR. TREANOR: This is the slide you are talking about, right? So day zero is the day when they come in. For particularly older people like these, they do have substantial amount of antibody that can be detected before they are vaccinated. So clearly those previous experiences that you have as an adult with multiple exposures to flu, and for most of these people, multiple prior vaccinations, do give you some level of antibody that can be measured prior to the vaccine, for sure.

DR. DEBOLD: The last question is, why is there so much more protein in your vaccine than in the GID?

DR. COX: When Dr. Treanor presented the overview of study PSC01, which was the dose escalation study, where we looked at 15 microgram of the H1 and 15 microgram of the B component, we determined that we would be able to have a potentially better vaccine if we would increase that antigen concentration threefold.

So we made a conscious decision, especially for an older population where you want to induce a strong immunological response to develop a vaccine that has a higher antigen content.

If you take a look at total protein content, as you know, the licensed vaccines that are made in embryo chicken eggs are not very highly purified. So if we take a look at total protein content, or other proteins but not necessarily

hemagglutinin, the protein content is very similar between the two vaccines.

The difference between the vaccines is that all the protein that is present, or the majority of the protein that is present in our vaccine is hemagglutinin and not other derived viral proteins, et cetera.

DR. DEBOLD: Thank you.

DR. FLEMING: Dr. Treanor and Dr. Cox, I'd like to think through the logic here of what you have shown us, which is very informative, relative to what you mentioned up front when you had defined your proposed indication, which wasn't specific to egg allergic subjects; it was a general indication.

It did include type B as well as type A, and it does include patients above 50. The reason I am making those distinctions is, if we could go to slide 107, I am following the logical pathway here, the anchor here is PSC04 which is a placebo control trial, which is the only powered efficacy trial. I am going to focus on type B. There is no data on the primary end point in type B, it is zero events against zero events. But you have an exploratory analysis which always has to be interpreted with caution, but it shows five fewer events with a modest efficacy of 23.1 that is not close to being significant.

So from an efficacy perspective, there is no

primary end point data, but there is an exploratory analysis that suggests a small level of protection, but by no means significant, not even close to significant.

Now, to extrapolate that, although we are extrapolating from a very weak anchor here, to extrapolate that to patients that are 50 to 64 and people who are above 65, you are using the PSC06 and PSC03 data. So if you go to slide 95, in essence the more strong value here, stronger value here, is in the setting where you had the actual known efficacy, which is an estimate of 23 percent that is not close to significant.

When you then try to extrapolate it to the 50 to 65-year-olds, you don't meet the criterion. When you try to extrapolate it to the over 65-year-olds, you don't meet the criterion even though Fluzone does.

Then if you go to slide 87, you mention in the lower right-hand bar, even though it wasn't a particularly impressive seroconversion rate on the active comparitor Fluzone, it did meet non-inferiority. Yours didn't. In fact, I think the words that you used is that this does not quite meet the non-inferiority when you are comparing in the lower corner in the B non-inferiority in these patients who are above 65. Well, it is actually even statistically significantly worse. So it is statistically significantly worse than active comparitor that wasn't that particularly

impressive.

So if I am following the logic, as I am trying to understand the justification for the inclusion of Bs, your anchor is the 04 trial. The 04 trial had no events on your primary end point. The exploratory analysis had some events, but with a very modest efficacy estimate that wasn't close to statistical significance.

But then, if you could just show one more time slide 95, that was in a setting where you actually had achieved the immunogenicity margins, the immunogenicity bar, for seroconversion. So we are now trying to extrapolate a weak result to the older patients, and we fail in being able to achieve that extrapolation, and in fact are significantly worse than Fluzone in the patients that are above 65.

Have I misinterpreted any of these data?

DR. COX: I want to make a number of comments, because I do think it is important to put the data in perspective.

First of all, as Dr. Treanor pointed out, in 2007-2008 in the efficacy study, the B viruses that were isolated all belong to a different lineage. If we take a look at our clinical studies with licensed vaccines, where we look at efficacy when there is a B mismatch, we will see efficacy. The Marsh Group study showed a negative efficacy against the B.

So the 23 percent, while not statistically significant, you are correct, does compare favorably with results with the licensed vaccine.

DR. FLEMING: Although you are extrapolating now to make comparisons for which you have direct head to head data, which are treacherous.

DR. COX: We will come back to that. I also want to point out that the end points in PSC04, while they are referred to as exploratory, they were predefined. In any situation where we are dealing with an influenza vaccine and where circulating viruses might not be -- and in most instances this is unfortunately the case, where the circulating viruses might not be represented in the vaccine, it is important to take a look at how --

DR. FLEMING: Of course, of course. Every clinical trial has primary end points. Those are the ones for which you can understand point estimates without random high bias regression, mean bias. Those are the ones for which you can understand P values.

I don't understand what a P value means for an exploratory analysis. We generate them, but they are very descriptive. So I don't think you are changing anything of what I am saying. Have I misinterpreted anything in what I have said?

DR. COX: I think it is very important --

DR. FLEMING: In a different context.

DR. COX: I do think it is very important to realize that PSC03 does not make a direct comparison. We are looking here in the FluBlok recipients who received B/Ohio, whereas the Fluzone recipients received the Malaysia, which is a different antigen. So it is very hard to make a --

DR. FLEMING: So it is fair to say, it would be a strong statement to say it is inferior, even though it is statistically inferior, I grant that.

DR. COX: I agree with you.

DR. FLEMING: But we are using these data as a basis to justify your very broad claim. That broad claim includes a claim for influenza B, including in elderly patients. I am just following the logic. Your best argument here is, don't take those data with great reliability because of valid things that you are saying. But on the other hand, Congressional law indicates that we approve based on substantive evidence, not on explaining away evidence that is favorable.

Let me ask one other quick question. That is on slide 52. It makes sense to focus on the second column, the 135, because we have a lower dose, except as you very nicely laid out, in the 75 it is the same dose in H3 and 2.

DR. COX: Right.

DR. FLEMING: So the categories where there were

the lower doses, H1N1 and B, there were no events. So if you have given the full 135 in those 150 people, you couldn't have possibly expected a better result than no events.

So I don't want to make a lot of this, because PSC01 was just a phase II trial. But I don't want to come away with estimates of 90 percent or 100 percent efficacy. Those four events count. Those four events occurred in a cohort in which the patients received the full 45 dose.

DR. COX: And that is why Dr. Treanor presented the data in a compiled fashion. But I do want to point out that interestingly, as you increase the antigen content of H1 and B, interestingly the GMT against the H3 also slightly rises. So that might have some impact here. I would agree with you that it is better to put the data together.

DR. FLEMING: It is possible, but in essence I think the takeaway that I would want to come from this is, this was serving as a phase II trial. The best estimate I come up with is one FDA gives, which is 68 percent efficacy, which does probably motivate the design of the 04 trial, which was 70 percent efficacy. It was designed for 70 percent efficacy, and actually got 44 percent efficacy.

DR. KOHBERGER: Put up the slide for B seroprotection. I am Bob Kohberger. I am the statistical consultant for Protein Sciences. If you look at seroprotection, yes, seroconversion does show differences and

possible problems. But seroprotection for B in the elder age group PSC03 is up around 90 percent. So that is another piece of evidence.

DR. FLEMING: These are all surrogates, so they are all incredibly weak evidence, anyway. The anchor of this is 04, which is efficacy. But surrogates, as I understand FDA having defined them, is seroconversion and seroprotection.

DR. STAPLETON: Dr. Eickhoff, you had a question?

DR. EICKHOFF: A couple of questions. First a comment o the subject that Tom Fleming was raising.

Clinical data supporting efficacy of the B component, not serologically, but the clinical data supporting efficacy of influenza B component of vaccine, is pretty few and far between. You have got to search high and low to find good clinical data supporting the efficacy of the B component.

That aside, a couple of questions for Dr. Cox. You made the comment back in describing TIV that one egg equals one dose. I have heard that from other sources, but I simply never thought to ask the question. Do you know if that one egg equals 15 micrograms of hemagglutinin or 45 micrograms?

DR. COX: I would imagine it is 45. It is obviously an average number. It is a trivalent vaccine.

DR. EICKHOFF: Yes, that is what I was driving at. Then a couple of questions for John, if I might.

In PSC04, it may have been 03, the large scale trial, this was a multi-center trial, I would assume, is that correct?

DR. TREANOR: Right, yes. I think there are maybe 12 centers in it.

DR. EICKHOFF: Twelve centers.

PARTICIPANT: Twenty-four.

DR. TREANOR: Twenty-four.

DR. EICKHOFF: From all over the country?

DR. TREANOR: Yes.

DR. EICKHOFF: And the central lab was the Cincinnati laboratory?

DR. TREANOR: Yes.

DR. EICKHOFF: You described 20 pregnancies that occurred in that group.

DR. TREANOR: Yes, in the recipients of FluBlok. There were additional pregnancies in the placebo recipients.

DR. EICKHOFF: Okay. If women were obviously pregnant -- or were pregnant women screened out?

DR. TREANOR: Yes, oh, yes. These were women who became pregnant after they were vaccinated.

DR. EICKHOFF: So they were largely in the first trimester of pregnancy.

DR. TREANOR: Yes.

DR. EICKHOFF: And of those that finally delivered

that you could follow, these were perfectly normal pregnancies?

DR. TREANOR: There were 15 of the 20 that were able to be followed to delivery. Of those 15, ten of them had normal pregnancies and delivered fullterm infants. Two of them had spontaneous abortions. One of them had an elective abortion because she had developed some other issue that she decided to have an abortion. Two of the pregnancies were complicated. One person had hyperemesis and I forget the other, but delivered normal babies. There were no birth defects noted.

DR. EICKHOFF: Then the follow-up question is directed at Dr. Cox. Were those vaccines to be licensed, what would the label say about pregnancy and this vaccine?

DR. COX: That would still be under discussion with the agency. In principle, we did not formally study this vaccine in pregnant women, so I think it would be excluded for pregnant women. But again, I am speaking ahead of what our discussion with FDA may bring.

We did conduct a reproductive tox study in rats, and that has all resulted in acceptable results. But that is obviously a model system that doesn't really compare to safety in humans. So this could either be a postmarketing commitment or subject to further discussions.

DR. EICKHOFF: Thank you.

DR. DeSTEFANO: Seasonal vaccines contain a neuraminidase antigen. I am just curious as to the implications not including a neuraminidase in this vaccine.

DR. COX: In principle, if you look at the two surface antigens of the influenza virus, there is hemagglutinin and neuraminidase. And hemagglutinin has been associated with protection against influenza, whereas neuraminidase and also the neuraminidase inhibitors, they are potentially reducing the impact of influenza.

What we see with the licensed vaccines is that the vaccine is not standardized to contain a certain amount of neuraminidase, because this is a highly labile protein, and in the manufacturing process it very often gets destroyed. So there are no real good measures of correlates of neuraminidase being present in the vaccine.

What we see is that there is efficacy with the vaccine without neuraminidase, as shown in study PSC04. At the same time, we have also many years ago in collaboration with NIH conducted some studies where, be it in very small populations, we added recombinant neuraminidase to a licensed vaccine. Again, very small subject numbers, only 30. What we did observe, if you added two and a half microgram of neuraminidase, you did see a small trend towards reduction of impact of disease.

So in other words, people that received TIV still

got sick when you challenged them with a virus. With the addition of two and a half micrograms of recombinant neuraminidase, you were able to reduce the impact.

So that is a long story to tell you that I think a next generate vaccine could contain a neuraminidase additive. But it is already quite a challenge on an annual basis to make a recombinant vaccine that contains three hemagglutinins that can be changed from year to year. So if you would add the neuraminidase to that picture, you would make it very complicated.

The question would be, do you have to adjust them on an annual basis. When you are going to formally add neuraminidase to the vaccine, are you going to induce more changes in that neuraminidase antigen, et cetera.

So we have said this is a very important observation that we made, but it is really something to be addressed in the future.

DR. STAPLETON: Dr. Eickhoff, you had another question?

DR. EICKHOFF: Well, more a comment. There is a school of thought that predicts that in subsequent years the pandemic H1N1 virus will in fact become seasonal flu. It happened in 1918, it happened in 1957, it happened in 1968. There is considerable support for this from historical seroepidemiologic studies that have been done. We will

probably get a hint about that in the next months when the presumed winter-spring wave of influenza starts. If it is H3N2, that is one thing. If it is H1N1 again, pandemic H1N1, that is still a different thing.

So my question directed at Protein Sciences folks is, do you have any studies either in progress or planned using the pandemic H1N1 virus?

DR. COX: We have in fact conducted a study in Australia in collaboration with a company called Vaxine, Dr. Petrovski. He might be here this afternoon and he might be able to make some comments. That study, the manuscript is in preparation. What it basically shows is that the H1 component of the vaccine behaves very similar to what one would expect of a seasonal influenza vaccine component.

We have recently been awarded a fairly large contract by Human Health Services that is going to help Protein Sciences to develop a pandemic vaccine candidate. We are in discussions with the HHS to determine whether it makes sense to conduct further studies with monovalent H1 or whether we should just accept that next year the H1 component will be part of the seasonal vaccine. That is the recommendation that Australia has made for the Southern Hemisphere, and it is quite likely that that might also happen here. Then it may not make sense to do a monovalent study. You might want to do a trivalent study.

DR. MC INNES: I have a question for Dr. Treanor. On the PSC04 study on your additional safety data that you show on what I have as 38 in the hard copy version, you are discussing unsolicited adverse events.

DR. TREANOR: This one here, right?

DR. COX: That's correct.

DR. MC INNES: John, the concept of subjects withdrawing in a single dose study is a little strange to me. I want to just know procedurally, those nine subjects received their dose of vaccine, developed an unsolicited AE, and then they were lost to follow-up? What do you mean by withdrew in that context?

DR. TREANOR: We can look at the clinical study report to verify this, but I think this means these are people who showed up and said, I don't want to make any more study visits because I've got other things to do. So they did not come back. They didn't get their blood drawn for day 28. I think that is what that means. Peter can verify this from the clinical trial report.

DR. MC INNES: Just because it is important to know whether they were followed for safety and for resolution. If seven of those are in your pregnancy group, then I am just wanting to know how that relates to the outcome.

DR. TREANOR: Right. Those seven pregnancies are not all in the FluBlok group.

DR. MC INNES: No, I understand, but they are in the study.

DR. TREANOR: Yes.

DR. STAPLETON: I have another question for you, John. The data you showed from PSC03 gave some later samples of antibody titers. Do you have a feeling for how long after what the duration was in those? And do you have later samples, six month, 12 month?

DR. TREANOR: No. That study was done to get a sample at the end of the influenza season, which was around May. So this would represent something on the order of six to seven months after vaccination.

DR. STAPLETON: Just a comment. One of the speakers mentioned this would be the first cell culture derived influenza vaccine in the U.S. That is true, but there have been other --

DR. TREANOR: Yes.

DR. STAPLETON: Any other questions from the committee? If not, we are a few minutes ahead of schedule. We will take a break and return at 11:10.

(Brief recess.)

Agenda Item: Safety and Effectiveness of Purified Recombinant Influenza Hemagglutinin Vaccine for the Prevention of Influenza

DR. STAPLETON: I think we will plan to get started

on the second half of the morning's topics. Our next speaker will be Dr. Cynthia Nolletti from FDA, who will review for us the safety and effectiveness data on the Protein Sciences vaccine.

DR. NOLLETTI: Good morning, everyone, and thank you, Dr. Stapleton. My name is Cynthia Nolletti, and I will be presenting the clinical data submitted in support of the FluBlok license application for the FDA this morning.

I am going to start with a summary of the product, followed by clinical overview, clinical data from the clinical trials, a brief recap of efficacy and immunogenicity, an overview of safety, overall conclusions, and finally questions for the committee.

The product as you have already heard is a trivalent recombinant hemagglutinin influenza vaccine consisting of three recombinant influenza hemagglutinin antigens derived from H1, H3 and B strains, inserted into a baculovirus vector and expressed in *Spodoptera frugiperda* insect cells. The proper name is influenza vaccine, recombinant hemagglutinin, and the proprietary name is FluBlok.

The proposed indication is for the active immunization of adults 18 years of age and older against influenza disease caused by influenza virus subtypes A and type B represented in the vaccine.

The dosage will be 135 micrograms of influenza hemagglutinin antigen, 45 micrograms per influenza strain, for each five milliliter dose. The vaccine is administered as a single dose intramuscularly.

Dr. Pandey has already reviewed the regulatory history, so we will skip this slide.

Data from four clinical trials, one phase II and three phase III trials, were submitted in support of approval of the 135 microgram dose. Two placebo controlled and two active controlled trials comprise the BLA.

The safety population consists of 3,233 FluBlok recipients, 23 percent of whom were 50 years of age or older, 13 percent of whom were 65 years of age or older.

The vaccine efficacy population consists of 2,344 FluBlok recipients, all of whom were 18 to 49 years of age. The immunogenicity population consists of 1,323 FluBlok recipients, 55 percent were 55 years of age or older and 32 percent were 65 years of age or older.

This slide summarizes the four clinical trials and their design. You have heard a lot of this already. There were two trials, PSC01 and PSC04, conducted in adults age 18 to 49, one trial, PSC03, conducted in adults 65 years of age and older, and one trial, PSC06, conducted in adults age 50 to 64. All trials were randomized modified double blind and multi-centered conducted in the United States. The largest

clinical trial was PSC04.

This slide summarizes our immunogenicity assessments. Immunogenicity end points were assessed using the hemagglutinin inhibition assay, an FDA criteria for acceptable immune responses. These criteria were published in our Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines, in May of 2007.

Although there is on established immune correlate of protection, the hemagglutinin inhibition or HI response may be an acceptable surrogate marker of activity that is reasonably likely to predict clinical benefit.

I just want to emphasize that the titer of greater than or equal to one to 40 is not equivalent with seroprotection. This is a surrogate marker of protection. Previous studies have suggested that HI titers of greater than or equal to one to 40 correlate with protection against illness.

The HAI assay in influenza viral cultures, nasal swab and throat swabs, were performed at a single central laboratory. A validated assay using baculovirus expression vector system or BEVS derived antigens was used to test sera from all treatment groups in all three phase III studies. Egg-derived antigens were used in the phase II study.

This slide summarizes the immune response end

points used in placebo controlled single arm studies. The seroconversion rate is defined as the proportion of subjects with either a pre-vaccination or baseline HI titer of less than one to ten, and a post vaccination titer of greater than or equal to one to 40, or a pre vaccination HI titer of greater than or equal to one to ten and a minimum fourfold rise in the post vaccination titer.

The second immune response end point that we assessed is the proportion of subjects achieving a post vaccination HI titer of greater than or equal to one to 40. The HI titers were drawn on days zero and 28 in all studies.

This slide summarizes the FDA's immune response acceptance criteria for these end points. For adults less than 65 years of age, the lower bound of the two-sided 95 percent confidence interval for the seroconversion rate should meet or exceed 40 percent, and the lower bound for the proportion of subjects achieving a post vaccination HI antibody titer of greater than or equal to one to 40 should meet or exceed 70 percent.

For adults 65 years of age and older, this lower bound on the seroconversion rate should be at least 30 percent, and the lower bound for the post vaccination HI titer of greater than or equal to one to 40 should be at least 60 percent.

This next slide summarizes the non-inferiority end

points and acceptance criteria that we use to assess active control trials. The first non-inferiority end point is the GMT ratio of a licensed trivalent inactivated influenza vaccine to FluBlok, 28 days post vaccination for each vaccine strain. The upper bound of the two-sided 95 percent confidence interval on this GMT ratio should not exceed 1.5.

The second non-inferiority end point would be the difference between the seroconversion rates of trivalent influenza vaccine and FluBlok. The upper bound on this difference should not exceed ten percent.

For the clinical efficacy end point, absolute vaccine efficacy relative to placebo was assessed in young healthy adults in studies PSC04 and PSC01. Vaccine efficacy was calculated as one minus the relative risk multiplied by 100, where the relative risk was calculated as the proportion of FluBlok recipients who developed culture confirmed influenza-like illness divided by the proportion of placebo recipients who developed culture confirmed ILI.

For the active control studies, PSC06 and PSC03, the relative efficacy or percent relative reduction of FluBlok to Fluzone was calculated using descriptive statistics as one minus relative risk multiplied by 100.

Influenza-like illness or ILI was assessed using a flu symptom scoring card in all studies. Subjects were to contact the clinic if they scored two or more points for any

of the following: one point was assigned for fever greater than or equal to 100 degrees Fahrenheit orally, one point could be assigned for cough or sore throat or runny nose/stuffy nose, and one point could be assigned for muscle or joint aches, headache, chills, sweats or tiredness/malaise.

CDC ILI was defined as fever of greater than or equal to 100 degrees Fahrenheit orally, accompanied by cough and/or sore throat on the same day or on consecutive days. ILI was monitored by both active and passive surveillance for six months and/or until the end of the influenza season, whichever was longer, in all studies.

I am going to discuss the largest clinical trial, PSC04, conducted in subjects 18 to 49 years of age now.

This study was conducted in the influenza season 2007-2008. It was a phase III placebo control trial of safety and efficacy in healthy young adults 18 to 49 years of age. The primary objectives were safety to determine safety relative to placebo, and efficacy to determine efficacy relative to placebo. Secondary objectives related to immunogenicity to assess immune responses to FluBlok according to acceptance criteria.

The study was a phase III prospective randomized double blind placebo control trial involving 4,648 healthy adults aged 18 to 49 years of age at 24 U.S. sites. Subjects

were randomized one to one to receive FluBlok or placebo. An immunogenicity subset of 480 FluBlok recipients at five sites was selected for the immunogenicity analyses.

Reactogenicity events were collected through day seven, unsolicited adverse events through day 28, and serious adverse events through day 180.

The primary efficacy end point was the proportion of subjects in each treatment group with culture confirmed CDC defined ILI associated with isolation of an influenza virus antigenic resembling vaccine strains, otherwise known as matched strains. Vaccine efficacy we said was calculated as one minus relative risk multiplied by 100.

The study was powered to assess the lower bound of the two-sided 95 percent confidence interval of vaccine efficacy around the point estimate of 70 percent. The acceptance criteria that was used was at the lower bound of the 95 percent confidence interval for vaccine efficacy of FluBlok relative to placebo should be at least 40 percent.

Secondary and exploratory efficacy end points included the following: one, proportion of subjects with culture confirmed ILI, not necessarily CDC defined ILI, due to matched strains; two, proportion of subjects with culture confirmed ILI due to any influenza virus strain, matched or mismatched.

Immunogenicity end points were the seroconversion

for each vaccine strain, and again the proportion of subjects with a day 28 post vaccination HI titer of at least one to 40 for each vaccine strain.

This guide summarizes the disposition of subjects in the study. One hundred percent of enrolled and randomized subjects were vaccinated, 88 percent of placebo recipients and 87 percent of FluBlok recipients completed the study. Fewer than one percent of subjects in either treatment group were discontinued because of death or adverse events, and there were 12 percent of subjects discontinued in the placebo group, 13 percent discontinued in the FluBlok group, most of whom were discontinued because of loss to follow-up, 11 versus 13 percent.

This slide describes the efficacy results in 18 to 49-year-old. 646 swabs were collected from 583 subjects obtained during the 180-day surveillance period. Sixty-four or 2.7 percent of FluBlok subjects and 114 or 4.9 percent of placebo recipients had culture confirmed ILI. The 2007-2008 vaccine strains were poorly matched to circulating viral strains in this season.

170 of 178 total isolates were antigenically mismatched. 111 of 119 type A isolates were antigenically mismatched or not typed, and 58 of the 59 B isolates were mismatched, of a different lineage; one was not typed.

This table illustrates the vaccine efficacy

results. According to treatment group, FluBlok in this column, cases of ILI in FluBlok recipients in this column, and cases in the placebo group in this column. If you look at the first row here shaded in green, you can see that all matched strains were of the H3N2 subtype. There were two cases in the FluBlok group and six cases in the placebo group. So if we look at the primary end point of CDC defined ILI for matched strains, we have a total of one case in the FluBlok group, four cases in the placebo group for a vaccine efficacy of 75.4 percent but with very wide confidence intervals that include zero.

If we look at all cases of culture confirmed influenza regardless of antigenic match, again you see that there are 64 cases in the FluBlok group, 114 cases in the placebo group, for any ILI. So down here the rate in the FluBlok group is 2.7 percent, the rate in the placebo group is 4.9 percent, for a total vaccine efficacy of 44.8 with a lower bound of 24.4 percent and an upper bound of 60 percent.

Looking at the specific strains, there were three cases of H1N1, nine cases in the FluBlok recipients, nine cases in the placebo recipients. There were 33 cases of H3N2 in the FluBlok group, 58 in the placebo group. There were five cases of untyped type A influenza in the FluBlok group and 12 cases in the placebo group. There were also a large number of type B influenza, 23 cases in the FluBlok

recipients, 36 in the placebo group.

If we look at type A ILI regardless of antigenic match and regardless of whether the influenza met the CDC case definition, the incidence in the FluBlok group was 1.7 and in the placebo group 3.4 for a vaccine efficacy for type A ILI of 49 percent, with a lower bound of 24.7 percent. If we look at type B isolates, the vaccine efficacy was 37.2 percent, but again the confidence intervals are wider and the lower bound includes zero.

To summarize vaccine efficacy in study PSC04 in adults age 18 to 49 years, vaccine efficacy results for FluBlok against culture confirmed ILI due to antigenically matched strains is limited by the small numbers of cases. The point estimate of vaccine efficacy against culture confirmed ILI for all strains regardless of antigenic match was 44.8 percent. The lower bound of vaccine efficacy for type A strains was 24.7 and for type B strains included zero.

This slide now summarizes the immunogenicity end point results according to each end point, seroconversion rate and proportion of subjects with a post vaccination HI titer of greater than or equal to one to 40 by antigen strain.

For the seroconversion rate, remember that the acceptance criteria is that the lower bound of the 95 percent confidence interval should be greater than or equal to 40

percent. So here, for each strain in the first line we have the point estimate of seroconversion rate and underneath the 95 percent confidence interval, and the lower bound is in bold type for each strain H1, H3 and B, was greater than 40 percent. So all three strains met this immune response end point of seroconversion rate.

Looking at the second immune response end point, proportion of subjects with post vaccination titer of greater than or equal to one to 40, where our acceptance criteria or target is that the lower bound of the 95 percent confidence interval should be greater than or equal to 70 percent, each strain met this end point as well, was more than 70 percent. So all three strains met both immunogenicity end points in this study.

I am going to move on to study PSC06, conducted in subjects 50 to less than 65 years of age.

This study was a non-inferiority comparison of FluBlok to Fluzone in healthy adults age 50 to 64 years. The safety objective was to compare the safety and reactogenicity of FluBlok and Fluzone. The efficacy objective was to compare the relative efficacy of FluBlok and Fluzone in the prevention of culture confirmed ILI, and the immunogenicity objectives included to compare the immunogenicity of FluBlok and Fluzone according to pre-specified non-inferiority criteria.

The study was a phase III prospective randomized double blind active control trial involving 602 subjects at five sites in California and Hawaii. Subjects were randomized one to one to receive FluBlok or Fluzone. Reactogenicity events were collected through day seven, unsolicited AEs through day 28, and serious adverse events through day 180.

Efficacy end points included proportion of subjects with culture confirmed ILI due to matched strains and the proportion of subjects with culture confirmed ILI regardless of antigenic match. Statistical analyses for the clinical end points were descriptive.

The non-inferiority end points for this study included the GMT ratio of Fluzone to FluBlok 28 days post vaccination for each vaccine strain, and the upper bound of the 95 percent confidence interval on this GMT ratio should not exceed 1.5. The difference between the seroconversion rates of FluBlok and Fluzone was the second non-inferiority end point. Again the upper bound on the 95 percent confidence interval should not exceed ten percent.

This slide describes the efficacy results. There were no antigenically matched isolates. The total numbers of antigenically mismatched isolates was small in both groups. For FluBlok there were seven cases and Fluzone four cases. These case numbers are too small and the confidence intervals

too wide to draw meaningful conclusions regarding the relative risk of influenza illness in recipients of FluBlok compared to Fluzone in healthy adults 50 to 64 years of age.

Because the clinical end point data in this age group was not adequate, the immunogenicity data provided an important surrogate marker of clinical benefit which is described in this next slide. The immunogenicity results for the first non-inferiority end point of GMTs and GMT ratio of FluBlok to Fluzone at day 28 is described here according to antigen up at the top. Here in the first set of rows are the GMTs on day zero for Fluzone and then FluBlok underneath.

In this next set of rows we have the GMT results on day 28 for Fluzone on the top and FluBlok underneath. In the next row we have the upper bound of the GMT ratio on day 28 where we would like to see this upper bound less than 1.5. For each strain, each antigen, the non-inferiority criteria was met.

The next slide summarizes the difference in seroconversion rates on day 28. Here in the first column you have the seroconversion rate point estimates, the lower bound of the confidence interval for each strain. Here I am going to focus your attention on the non-inferiority end point, the difference between those seroconversion rates, where the upper bound should be less than ten percent. The upper bound on the confidence interval for this difference is in bold

type. Each strain met the non-inferiority criteria for difference in seroconversion rate.

To summarize, FluBlok met all six end points establishing non-inferiority to Fluzone in this study of 50 to 64-year-olds.

The next study was PSC03, conducted in subjects 65 years of age and older. This study was a non-inferiority comparison of FluBlok to Fluzone in adults 65 years of age and older. The safety objective was to compare safety and reactogenicity of FluBlok and Fluzone. The efficacy objective, or one of them, was to compare the relative efficacy of FluBlok and Fluzone in the prevention of culture confirmed ILI. The immunogenicity objective was to compare the immunogenicity of FluBlok and Fluzone.

This study was a phase III prospective randomized double blind active controlled study involving 870 medically stable adults 65 years of age and older at six U.S. study sites. Subjects were randomized one to one to receive FluBlok or Fluzone. Safety events were collected as for PSC01 and PSC06.

The efficacy end points for this study included the proportion of subjects in each vaccine group who experienced culture confirmed CDC defined ILI, and the proportion of subjects who experienced any culture confirmed medically attended acute respiratory illness. Descriptive statistics

were used to calculate the relative efficacy of FluBlok to Fluzone.

The non-inferiority end points for this study were the GMT ratio of Fluzone to FluBlok and the difference in seroconversion rates.

This slides describes the clinical efficacy results for this study in older adults. Of 53 sets of cultures, only three were positive, two in the Fluzone group and one in the FluBlok group. All three were influenza type A. Once again, the case numbers are too small and the confidence interval is too wide to draw meaningful conclusions from study PSC03 regarding the relative risk of influenza in recipients of FluBlok compared to Fluzone, in adults 65 years of age and older.

This slide summarizes the GMTs and GMT ratios in adults greater than 65 years of age by antigen strain on day zero in the first two rows., day 28 GMTs in these next two rows, and then shaded in green we have the upper bound of the GMT ratio on day 28 for each antigen. Again we want the upper bound to be less than 1.5 to establish non-inferiority.

For H1 and H3, the upper bound is indeed less than 1.5, meeting non-inferiority criteria. I'm sorry, for all three strains the upper bound was less than 1.5.

Moving on to the difference in seroconversion rates at day 28, here we have each vaccine strain. Here in the

first green column is the difference of seroconversion rates between the treatment groups and the 95 percent confidence intervals are in parentheses, with the upper bound of the confidence interval in bold type. This upper bound should be less than ten percent. Here for this end point, H1 and H3 did meet non-inferiority criteria, but the B strain failed to meet the criteria. The upper bound was 16.1 percent.

So to summarize the immunogenicity end point results in the elderly, subjects 65 years of age and older, FluBlok met five of the six primary end point criteria for demonstrating non-inferiority to Fluzone. H1 and H3 antigens met both non-inferiority end points. These strains demonstrated non-inferiority to Fluzone by the GMT ratio, but not by seroconversion rate criteria.

The fourth study was PSC01, conducted in subjects 18 to 49 years of age. This was the earliest study conducted in 2004-2005 influenza season. It was a phase II dose finding safety, immunogenicity and efficacy study in healthy adults age 18 to 49 years.

The safety objective was to determine safety relative to placebo. The immunogenicity objective was to compare the immunogenicity of two dose levels of FluBlok, 75 micrograms versus 135 micrograms of total hemagglutinin antigen. The efficacy objective was to determine clinical efficacy in the prevention of culture confirmed influenza-

like illness.

As you remember from Dr. Treanor's talk, the 75 microgram dose contained 15 micrograms of H1 antigen, 45 micrograms of H3 antigen, and 15 micrograms of B, as opposed to the 135 microgram dose which contained 45 micrograms of each antigen. So H3 is equivalent in the two dose levels.

A clinical efficacy end point was the proportion of subjects with culture confirmed ILI. This study was not powered to test a formal null hypothesis. Descriptive statistics were used only to detect trends between the treatment groups.

This next slide presents the efficacy results in tabular form. Here in this column we have cases of influenza that occurred in FluBlok recipients and the total number of subjects for the 135 microgram dose group was 151. In this column we have placebo recipients for a total of 153 subjects.

If we look first at matched strains, we see that there were no cases. So if we then look at all isolates regardless of antigenic match and regardless of whether the influenza-like illness or culture confirmed influenza met the CDC definition, there were a total of one case in the FluBlok group and eight cases in the placebo group. Vaccine efficacy was 87.3 percent with a lower bound of 5.5 and an upper bound of 99.7 percent.

If we look at all cases of H3N2 for the 135 microgram group only, you will see that there were no cases in the FluBlok group, six cases in the placebo group, for a vaccine efficacy of 100 percent. However, if you look at both dose levels, if we include the 75 microgram dose level in the analysis, because both dose groups contained 45 micrograms of the H3N2 strain, we have a total number of 301 recipients, and in the FluBlok group we have four cases. In the placebo group we have six cases of H3N2, so the vaccine efficacy against H3N2 becomes 66.1, but with wide confidence intervals that include zero.

There were only three cases of B type influenza, one case in the FluBlok group, one case in the placebo group. So if we look at both dose levels of FluBlok, we look at all isolates, both dose groups, any ILI, matched, mismatched, we have a total of five cases in the FluBlok group and eight cases in the placebo group for vaccine efficacy of 68.2 percent, but this includes zero.

To summarize, antigenically dissimilar H3N2 virus predominated in this season. The vaccine efficacy of the 135 microgram dose was 87.3 percent with a lower bound of 5.5 percent against all culture positive ILI and against all strains regardless of match. Because H3N2 predominated and because both the 75 microgram and 135 microgram dose groups contained 45 micrograms of H3 antigen, if all cases from

subjects who received the 75 intervention dose are included in the analysis, vaccine efficacy decreased to 68.2 percent with a lower bound that includes zero.

So the estimates of vaccine efficacy in study PSC01 suggest a favorable trend. However, this study was not powered to test a formal null hypothesis of vaccine efficacy, and it is limited by the overall small sample size and wide confidence intervals.

This slide summarizes for you again the total database. All four studies, two conducted in younger subjects 18 to 49 years of age, and one conducted in subjects 50 to 64 years of age, one in subjects 65 years of age and older. The total immunogenicity population was 1,328 for the FluBlok recipients, and this is only for the 135 microgram dose. The total efficacy population was 3,231 subjects.

To summarize vaccine efficacy across studies, in PSC04, young healthy adults, despite antigenic mismatch, the overall vaccine efficacy against culture confirmed illness from any strain was 44.8 percent with a lower bound of 24.4 percent. Point estimates against all type A and all type B influenza were 48 percent and 37.2 percent respectively. This study failed to meet the primary end point against antigenically matched strains because mismatched circulating virus predominated.

With regard to study PSC01, also conducted in 18 to

49-year-olds, antigenic mismatch predominated exclusively. Descriptive statistics demonstrated a favorable trend towards vaccine efficacy with a point estimate of 87.3 percent against all culture confirmed ILI. This is for the 135 microgram dose.

For studies PSC03 and PSC06 in adults greater than or equal to 50 years of age, we were unable to assess relative efficacy because of very small numbers of cases.

For efficacy conclusions, in healthy adults 18 to 49 years, the vaccine efficacy of FluBlok against culture confirmed influenza due to antigenically mismatched strains was 44.8 percent with a lower bound of 24.4. The efficacy data is driven by study PSC04, adults 18 to 40 years of age, where the sample size and attack rate were adequate to assess absolute vaccine efficacy against placebo.

To summarize immune response and non-inferiority end points across clinical studies for the 135 microgram dose, H1 and H3 strains met both immune response end points in adults 18 to 49 years of age, studies PSC04 and PSC01. H1 and H3 strains met both criteria for non-inferiority to FluBlok in older adults in the two studies that evaluated non-inferiority end points, PSC03 and PSC06. The B strain met both immune response end points in the largest and pivotal study, PSC04, of young healthy adults.

The B strain also met both criteria for non-

inferiority to Fluzone in study PSC06, adults 50 to 64 years of age. B strain met the GMT ratio non-inferiority end point, but failed in the seroconversion end point for non-inferiority to Fluzone in study PSC03, adults 65 years of age or greater.

So for immunogenicity conclusions, FluBlok is immunogenic in young adults 18 to 49 years of age. The FluBlok H1 and H3 antigens also elicited a robust immune response that was non-inferior to Fluzone in adults 50 years of age and older. The B antigen failed to demonstrate non-inferiority in elderly adults 65 years of age and older. Similar weak responses to the B strain have been noted in studies of older adults using currently licensed trivalent influenza vaccines.

I am going to move on now to discuss safety results. This slides shows an overview of criteria across trials. These safety results pertain only to the 135 microgram dose intended for licensure.

The safety database for FluBlok 135 micrograms consisted of 3,233 subjects 18 to over 65 years of age. Twenty-three percent of subjects were greater than or equal to 50 years of age and 13 percent were 65 years of age and older. As you can see in the table, there was a predominance of females, slightly more females than males, in all four studies. This isn't presented in this slide, but Caucasians

represented the majority of subjects. In study PSC03, there was a slight over-representation of African-Americans and Latinos or Hispanics. In study PSC03 there was a slight over-representation of Asians -- that was conducted in California and Hawaii -- relative to the U.S. Census population.

Regarding deaths, there were a total of six deaths across the four studies, two occurring in young previously healthy adults in PSC04 and four appearing in subjects greater than or equal to 65 years of age in PSC03.

Here in PSC04 there was a FluBlok recipient who developed a pulmonary embolism on day 94 post vaccination. In the control group there was a motor vehicle accident that occurred 171 days post vaccination. Neither of these were considered to be related to the study vaccines.

In the elderly adults, in the FluBlok group there was one case of a perforated diverticulum with ensuing sepsis and death, and a case of pontine hemorrhage. In the control group there was one case of cardiac arrest and one case of coronary heart disease. Again, none of these were considered related to the study vaccine.

Overall, the deaths appear to be balanced, three in FluBlok recipients and three in control groups, and none appeared to be related to study vaccines.

This slide presents a summary of the serious

adverse events that occurred day 180 across trials. In the first two columns we have FluBlok recipients and in the last two columns control recipients.

Overall, the greatest number of SAEs occurred in studies PSC03 and PSC04. PSC04 was the largest trial. The greatest frequency of SAEs occurred in study PSC03 elderly adults. There were a total of 70 subjects who experienced 90 SAEs in the FluBlok group and a total of 71 subjects who experienced 90 SAEs in the control group. None of the SAEs were assessed to be related to the study vaccines in the control group on the basis of absence of temporal relationship or biological plausibility.

In the FluBlok group, there was one case of vasovagal syncope that was related to the study vaccine, and one case of pleuropericarditis that could have been possibly related to the vaccine.

The case of pleuropericarditis occurred in a 37-year-old male with a history of hypertension who had onset within 11 days of vaccination of FluBlok. Seven days after vaccination he experienced cough, fever, shortness of breath and pleuritic type chest pain. He saw his primary care doctor on day 11, had a stack echocardiogram which revealed cardiac tamponade and was hospitalized immediately. He underwent cardiac catheterization. He had pleurocenteses, test tubes, a pericardial window. Evaluation of the pleural

and pericardial fluids was undertaken. He had negative routine cultures, viral cultures, mycobacterial and fungal cultures. Serologies and viral titers were all negative. His discharge diagnosis was possibly viral pleuropericarditis, and the investigator's assessment was that this could possibly have been related to FluBlok.

The second SAE in the FluBlok group was that of vasovagal syncope that occurred in a 57-year-old male, who had onset within 15 minutes of phlebotomy and receipt of syncope. This report was not suggestive of an anaphylactic or hypersensitivity reaction. Rather it was compatible with vasovagal syncope that is sometimes associated with phlebotomy and/or intramuscular injection. The assessment of this event was that it was related to FluBlok.

This slide is kind of busy. It is a summary of all the serious adverse events by MedDRA system organ class or by body system. The only imbalance appeared in study PSC04, infections and infestations, where there were four events in the FluBlok group and 13 events in the placebo group.

The table is continued on this slide. If you just look at the totals, you can see that between treatment groups in each study, the overall number of subjects with SAEs and total number of events was balanced.

As part of the safety review, the data was evaluated for hypersensitivity events across studies.

Electronic data sets from each of the four studies were searched for hypersensitivity type reactions using MedDRA preferred terms. PSC was asked to provide case narratives, case report forms, and where available consulting physician's notes for all hypersensitivity type events.

This table summarizes the results of the search according to treatment group, FluBlok, placebo and Fluzone here, and then according to the preferred term.

I am going to start with rashes. There were nine events in the FluBlok group, three in the placebo group and six in the Fluzone groups. The rates were lower in the FluBlok group, 0.3 percent, compared to Fluzone, 0.8 percent. None of the rashes in FluBlok recipients were serious or severe, and the majority appeared unrelated to FluBlok.

Of the remaining hypersensitivity type events in FluBlok recipients, there were two events across studies that were either serious or severe, and that may have been related to FluBlok.

We have already discussed the case of pleuropericarditis. The second case was a case of swelling of the lips and tongue. This occurred in a 22-year-old female with a history of seasonal allergic rhinitis, exercise induced symptoms that were characterized by bronchiolar constriction, facial edema, edema of the extremities, rash, itching and swelling of tongue. She also had a history of

mild asthma and headaches.

This female had abrupt onset of swollen lips and tongue ten hours and 20 minutes following vaccination. She self medicated with Claritin or loratidine ten milligrams and Benadryl 25 milligrams. Her symptoms resolved by study day two. The investigator assessed this event as being moderate in severity and possibly related to the study vaccine.

To conclude, the safety database did not reveal other hypersensitivity type safety signals, and the data did not reveal large imbalances in these events between treatment groups.

This slide presents reactogenicity events across trials. It is a little busy, but here you have local reactogenicity events. These were collected through day seven. Down here we have systemic reactogenicity events. Here we have the treatment groups, FluBlok, Fluzone and placebo.

The most frequent events are shaded in green. In the FluBlok recipients the most frequent events were pain in 37 percent of subjects, headache in 16 percent, and fatigue in 14 percent and muscle pain in ten percent. These rates were similar to the FluBlok recipients, and local events were greater than in placebo recipients, but systemic reactogenicity event rates overall were not that much different from placebo.

This slide summarizes unsolicited adverse events which were collected through day 28 post vaccination. Overall rates were similar between the FluBlok and control groups. The most frequent events across studies were headache, which occurred in a range of .3 to 8.4 percent of FluBlok recipients, and symptoms of respiratory infection, which occurred in zero to 5.9 percent of FluBlok recipients. Most events were assessed as not related to the study vaccine, and most were mild to moderate in severity.

There were no unusual trends, patterns or safety signals overserved. There were no reports of Guillain-Barre syndrome or other autoimmune type events. The frequency of unsolicited AEs was similar to licensed trivalent influenza vaccines. The analysis of individuals over 65 years of age did not reveal safety issues unique to this age group.

Dr. Treanor had also mentioned a case of possible Bell's palsy that occurred in study PSC04. That was a very questionable case of Bell's palsy. It occurred in a female who had a history of recurrent Bell's palsy that was characterized by a prodrome of watery eyes instead of dry eyes, as you might expect to see in Bell's palsy. This female started having her watery eye symptoms one day before vaccination. Her syndrome was diagnosed within hours, so it is a little atypical for Bell's palsy, and did not appear to be related to FluBlok.

For safety conclusions, the safety database for FluBlok, 135 micrograms, consisted of 3,233 subjects 18 to over 65 years of age. Deaths were few, six in total, balanced, and appeared unrelated to the study vaccines. The vast majority of suicidal ideations occurred in subjects older than 65 years of age, and were assessed as unrelated to the study vaccines. Two serious adverse events in FluBlok recipients were related or possibly related to the vaccine, vasovagal syncope and pleuropericarditis. There was no large imbalance of hypersensitivity events, no other unusual trends, patterns or safety signals were observed, and overall the type and frequency of adverse events experienced by FluBlok subjects was similar to those reported for other trivalent influenza vaccines.

This slide presents overall conclusions. FluBlok demonstrated an absolute vaccine efficacy of 44.8 percent with a lower bound of 24.4 percent against antigenically mismatched influenza strains in healthy adults 18 to 49 years of age. FluBlok elicited robust immune responses to H1 and H3 and somewhat weaker responses to the B antigen in older adults.

The safety data did not reveal unexpected trends or safety signals, and the type and frequency of adverse events experienced by FluBlok subjects were similar to those reported for licensed trivalent influenza vaccines.

Shall I go on to reiterate the questions for the committee?

One. Do the available clinical data support the effectiveness of FluBlok in the prevention of influenza disease caused by influenza subtypes A and type B included in the vaccine in adults A, 18 to 49 years of age, B, 50 to 64 years of age, C, 65 years of age and older.

Two. Do the available safety data support the safety of FluBlok in adults 18 years and older?

Three. Please comment on what additional studies, if any, should be requested postlicensure.

DR. STAPLETON: Thank you, Dr. Nolletti. Are there any questions for Dr. Nolletti from the committee, or comments?

DR. FLEMING: There are a few issues here. Just to set context, I'll go quickly on some of these. Slide 20, if you could just follow with me quickly. I am just noting here that there is quite a large number of people lost to follow-up, a total of 546. We are usually uncomfortable with the number of people lost to follow-up exceeds the number of people having events, and it is multiple fold more than the number of people having events.

I have so many issues here, I'm just going to keep going. I am worried about whether or not that is uninformative. Missing this is usually informative.

Slide 22. I have already commented earlier about my particular concerns about the B strain efficacy being problematic. But it is noteworthy. This is the efficacy trial, this is the anchor, the 04 trial. This is the one study upon which we are getting direct evidence of efficacy. We focus traditionally on the primary end point. It is the one where you interpret P values, confidence intervals. Everything that is exploratory is much more problematic to interpret.

Unfortunately as you have already noted, there was a real mismatch this year. They were planning a three percent primary end point rate; they got one-fifteenth that level. So it is not negative evidence, but it is obviously a failed primary end point. The secondary end point is also a failed secondary end point. So we are looking at exploratory analyses. These lower confidence intervals of exploratory analyses need to be viewed with a lot more caution.

But with that as context, let me get into the safety. You have noted here that there are -- in fact, we might look at slide 61. Slide 61 gets into hypersensitivity type reactions. As you noted, numerically this isn't a huge excess, I definitely agree with that. But everything is benefit to risk. So the issue is, how important is this if it is real, and how biologically plausible is it. I know there is discussion about risk for contaminating residual

inside cell, proteins, et cetera that could be hypersensitivity reactions.

When we look at this, rash is nine to nine, but the others are seven to one. In particular those that were serious you referred to as the pleurocarditis and the vasovagal syncope, but particularly the first that induced the hospitalization. So there is substantial evidence that there is at least some excess here, but it is hard to know what the true magnitude is, but there is also this induced hospitalization.

But the question is, is that offset by the benefit? The benefit is, we have got 133 CDC ILI events, and we have 178 ILI events. I didn't see any indication of any of those led to hospitalization, is that correct? Is that your understanding as well?

DR. NOLLETTI: Well, they were not recorded as such, no.

DR. FLEMING: So by my calculations, looking at from a nationwide perspective, the number of influenza cases against the 220 hospitalizations, against the 36,000 deaths, by my calculation that is very consistent with what you would expect in this population. This preventing 30 to 40 influenza events in a 18 to 49-year-old category would lead to less than an expected one prevented hospitalization.

So when I look at the pleuropericarditis, it is one

event, but one induced hospitalization does trump no prevented hospitalizations, if this is reliable evidence. So my sense about how much emphasis I put on an event is always in the context of what overall efficacy is.

So in this 18 to 49 group, I have trouble interpreting the magnitude of the importance of this, but it does seem to at least parallel what you would expect the benefit to be.

Now, let me extrapolate now. Let's go on to the 50 to 65-year-olds and the above 65-year-olds. The sample sizes are so much smaller. Instead of having 2300 people that received FluBlok, it is 3,430, so it is about one-tenth. One-tenth is based on the fact that we are using a correlate. We are using the hemagglutinin inhibition correlate.

It is really important to be precise here. It is a correlate, but as you correctly point out, it is not an established surrogate. It is a correlate for risk of illness. It is not a correlate of protection. That infers causality. It is not a correlate of protection against illness, it is a correlate of risk of illness. The FDA as I think in essence set forward an understanding of that, because it is not being used for approval, it is being used to bridge if you have actually shown the approval of the efficacy in the lower age group.

Just a real quick illustration of this. Throughout

the '90s we had five pertussis vaccines. FHA and PT titers are clearly correlates. But they are not surrogates in that setting.

The issue that I want to get at though is, often when we rely on a correlate, we are ont only not getting the true efficacy answer in the 50 to 65-year-olds and the older than 65, but we are not getting the safety, either.

So this is a question for FDA. Just by using the rule of three, when you have 2300 people, as we do, that are treated in the 04 trial, you have sensitivity to safety events that are 1.3 per thousand. I.e., you can rule out something that in truth would occur more frequently than that, but you can't rule out something that is less frequent than that.

In fact, if we are saying we are preventing hospitalizations due to influenza-like illness, those would be inducing less than one per thousand. So it would seem you have got to have sensitivity to one per thousand. But then when you transfer to what you have in terms of reliable evidence from the 06 and 03 trials in the 50 to 64 and in the greater than 65 categories, you can't rule out events that are more than ten per thousand. It is the old, absence of evidence is not evidence of absence. I am getting the picture that we are not seeing a lot of evidence of bad things. We don't have the data to assess.

So one question for the FDA. If you say we are marginally able to rule out unacceptable safety risks in the 18 to 49 using the one large trial, why should we be comfortable extrapolating that safety experience to people 50 to 65 and in particular over 65? Anybody at FDA.

DR. STAPLETON: Dr. Nolletti, would you like to address it?

DR. NOLLETTI: You make a good point. The database in the older age group is smaller, so we can't say for sure that these events might occur with as lower frequency as in the younger adults.

DR. STAPLETON: Does anyone else at FDA wish to comment?

DR. FLEMING: My last issue is just a clarification for me. My understanding is, what is different about this vaccine that could be importantly positive. My understanding, which isn't perfect about this is, being a cell culture derived influenza vaccine, it could be formulated in a shorter period of time, which would at least theoretically allow the possibility that you could reduce the setting. But unfortunately they had in the 04 trial, where the isolates were antigenically mismatched in a huge fraction of cases.

So the very thing that I might think is particular useful about this vaccine in the setting in which it was

assessed was particularly mismatched. But let's say hypothetically they can match more effectively. Are we approving the vaccine in this formulation or we are approving the vaccine as it could be reconstituted annually in a more rapid time frame? But then if that were the case, how do you know what the efficacy of that reconstituted is?

So are we approving the vaccine in this exact configuration, in which case this advantage is hypothetical? It is not in fact causally important.

DR. STAPLETON: I will try and address that, and Dr. Baylor can correct me if I mis-speak.

I would say we are examining the data for this vaccine, and we are approving this vaccine. The other advantages or disadvantages are not what we are deciding today.

DR. BAYLOR: Let me just clarify that a little bit, because influenza is very different. What we are approving is how this vaccine is manufactured, the manufacturing process. Influenza vaccine changes just about every year, so we are going to change the strains whenever there is a need to change those strains based on surveillance data.

But as we change the strains, the manufacturing process will be this process, so that is what you are looking at: this manufacturing process to make this vaccine with the particular strains that will be circulating in those given

years.

So as we see these clinical trials, these are not the strains that are going to be circulating in the future. There will be other strains, but it is the manufacturing process used to make this vaccine.

DR. FLEMING: So that seems to be a different understanding. That seems to be the --

DR. STAPLETON: I don't think it is. I think we are examining the data of this product. Almost every year flu vaccine changes, and we don't go back and require efficacy trials for a drug because it is a new strain. Am I correct, Norman?

DR. BAYLOR: Right. You mentioned, Dr. Fleming, the configuration. The configuration will change. That is what happens. By configuration, I mean the strains may change, so that will happen. So recognizing that, we are saying the same thing. But keeping that in mind, the configuration will change, and we don't require additional clinical studies to change the configuration, i.e., the strains in the vaccine.

DR. FLEMING: So the manufacturing process we are approving and will stay the same. The configuration may change. I know in my past years with this committee, we always got together the last week of January and tried to provide guidance on that,

will that guidance be used if this vaccine is used, and then they would have to configure it according to what that guidance would say?

DR. BAYLOR: Correct. As we have done in the past, we have our February VRBPAC, and then depending on the WHO data and the worldwide surveillance data, it will dictate whether the strains should be changed or not. This committee will deliberate on that and make a recommendation. That recommendation if accepted by the FDA, which it generally is, will go to the manufacturers to formulate the vaccine with those particular strains, but not changing the manufacturing process.

DR. FLEMING: From a usefulness perspective, that makes sense. From a what it is we are approving perspective, it makes it even more complicated.

Just for clarification, my last comment that I should have mentioned when we had slide 22 up. My understanding of the FDA guidance document is that for efficacy, which is what we need here in order to get a full approval, for efficacy we need an estimate of sufficiently favorable magnitude with precision to rule out a lower limit of 40, 45 percent, is that correct?

DR. NOLLETTI: Right.

DR. FLEMING: So clearly it is not even close to that on primary or secondary. But even on exploratory

analysis, this analysis says 24, the analysis in CDC ILI is 18, is that correct?

DR. GELLIN: Because precision is important, I don't actually think we get to approve anything. We are advising how this works.

So I think we have to be careful about which A word we are using. We are advising on the questions. I think the questions brought us back to what we are trying to do about data, because we slid into this approval thing, and that is not what we are doing.

DR. FLEMING: In fact, I so strongly agree with you, I don't understand why advisory committees vote. Advisory committees should be -- and I have been saying this to Temple for two and a half decades -- we should be here to provide advice and rationale, because the FDA makes the decisions.

DR. BAYLOR: I just wanted to clarify, our guidance is really for matched strains. Here we have a mismatched strain.

DR. NOLLETTI: I was going to say that as well. The guidance is that the lower bound on the confidence interval should be at least 40 percent, but that pertains to antigenically matched strains.

DR. FLEMING: It actually doesn't say that specifically in reading the guidance. It just says -- and I

am presuming it is referring to whatever you accept as the primary end point, which in this case was matched strains. But the lower limit is -148 and the other lower limits weigh in the negative as well. So these results don't rule out harm.

DR. LEVANDOWSKI: I have a question about what actually is matched and how that has been validated for this set of studies. Nobody is going to answer anything specific for you, but if you change the definition for what is a match, then you might have more data.

I'm not suggesting we can do that or do it retrospectively, but I think it is critical to understand what is a match . If it is H3N2 versus an H3N2 vaccine, is that a close enough match? I don't know, probably not.

Every time you have a new isolate, it is somewhat antigenically divergent from all the other isolates that are out there. Therefore, it is very important for the laboratory that making this decision as to whether it is a match or not, to be capable of interpreting that kind of information.

You are turning a spectrum of how close is it antigenically into yes-no. You can see why you want to do that for criteria of this nature, but it makes it a little bit tricky. The laboratory that is described in the information here is that it was the Cincinnati Children's

Hospital lab that did this, but I don't know if they had any backup support, validation for their methodology in determining what is a match or what is not a match. Maybe somebody could comment on that for us, just to clarify that a little bit.

DR. COX: We worked in close collaboration with CDC, and they provided the post infectious hyper immune serum, so we worked with them to determine how to best perform this study. And yes, the assays were all qualified and validated.

DR. ROMERO: A question on the lost to follow-up group and maybe some comment from the FDA. I haven't seen numbers like this before, over ten percent lost to follow-up. Is there some criteria as to the need for less than a certain number lost to follow-up for interpretation of the data?

As you go back to the issue of safety, you lost 13 percent in your treatment group in the pivotal trial, 11 percent of the pivotal group. But that is a little bit worrisome. In other words, can you really get some information out of this?

DR. STAPLETON: Would anyone like to comment on that?

DR. NOLLETTI: Those numbers concerned us as well. We can't do too much about them. We did ask for some detail

regarding those numbers, but didn't really have specific reasons.

DR. COX: May I make one comment? We worked with 24 sites. Some of them we had worked with before, and they had dropout rates of one to two percent. They were very experienced in working on influenza, with influenza.

Then we have a number of sites unfortunately where you have a disproportionate dropout rate. This is mostly in areas where people just enrolled in the study for the initial compensation they would receive or for the vaccine itself. So it was limited to five sites where you had huge dropout rates.

DR. FLEMING: I just may comment on some principles. It is hard to put a number on what is acceptable and what is not. I have always said high quality studies are really important, and they help products, because the fewer the irregularities, the lesser impressive the result has to be to be clearly established in spite of the noise.

While it is by no means a rule, my sense is, when the number that are missing exceed the number of events, then I am particularly concerned. It is two or threefold higher. But even that doesn't tell the final answer. It is how informative is the missingness.

The only missingness that I am ever confident is relatively uninformative is staggered entry missingness. You

are looking at time to event, people coming in uniformly over a time period, everybody is followed to a calendar date. Some people don't see the event because of censoring. That is generally uninformative missingness.

But if people are lost to followup because they are unhappy with how things are progressing, they are not taking the intervention and other factors like that. That tends to be often what is happening. They have side effects or whatever. That is highly informative missingness.

So it would be important to drill down and understand more what the causes are. But generally for this kind of lost to followup, it is informative missingness. It doesn't mean you cannot interpret the results, but it does mean that it adds just that much greater concern about the reliability of results when you have this much missingness.

DR. DEBOLD: A question about the pleuropericarditis patient. Can you talk a little bit about why there is the sense that this may be biologically plausible related to vaccine?

DR. NOLLETTI: For a traditional influenza vaccine, cases of pleuropericarditis would be unusual. We did look back at the VAERS data from 2001 to 2007 for cases of pleuro, pleuro effusions and pericarditis, and there were not many cases.

Of course, looking back at VAERS data is difficult

because there are many confounders, and there is no true denominator. But for a traditional trivalent influenza vaccine, that would be unusual. I can't think of biological plausibility. We were more concerned about it in this subject because of the insect cell line and the theoretical possibility that there might be some hypersensitivity. But honestly, I don't see the pathophysiology behind it.

DR. GELLIN: I had the same observation. I think we have one case. Men between 20 and 50 is when this event occurs normally. It is often idiopathic, so it is not like there was a hug workup. They came up with nothing, and so they said maybe viral, but maybe unsure.

So these events happen in time. The time frame from vaccination to event is striking, only because that is when often immunologic things make it again. But you can't figure this one out, but it does highlight maybe the need to continue to look for things like this.

In the smallpox program, there was a biological plausibility to myopericarditis because the virus does that. Therefore in the live virus like the vaccinia virus, that was something that made sense. While influenza viruses can do this, here we have a system where we don't have a diagnosis of influenza or anything that sounds like influenza in these patients, and you have a vaccine that doesn't have anything live in it.

So I think we are stuck with this one, and it is obviously a very tiny numerator over a pretty small denominator, of what is otherwise a rare event in life.

DR. ROMERO: This information may not be available. You mentioned that an attempt was made to culture a virus from the fluid that was obtained. The better question would be, was there an attempt to amplify viral genome that are known to be associated with this type of a syndrome. That would have answered this question.

DR. NOLLETTI: Serology is done and there were cultures done, but I don't recall PCR. I know there were no influenza viral cultures done specifically, but they looked for adeno, the entero viruses, et cetera.

DR. ROMERO: Serologically we know the limitations. The yield is very low. Jeff Tobin in Texas has looked at PCRs in these patients and has been able to amplify these viruses from there. So I think that would be a more telling test and maybe more reassuring, given the information that we have now.

DR. EICKHOFF: What year did that occur?

DR. NOLLETTI: This was 2007-2008.

DR. EICKHOFF: PRC technologies were beginning to become widely available at that point.

DR. NOLLETTI: I just wanted to say that to respond to Dr. Fleming about extrapolating the safety from the

younger population to the older adults.

I think from the medical point of view I don't see that hypersensitivity events would occur more frequently in elderly folk. If anything, the immune response wanes over time.

DR. FLEMING: There are two benefits that I see with the avoidance of over extrapolation. One is if we had on the order of 2500 per in the intervention group, in each of these three age cohorts, which as I see things is minimally sufficient, it would have allowed us to understand the hypersensitivity reactions overall more effectively, in addition to the avoidance of extrapolate.

But I am not just talking about hypersensitivity reactions. I am talking about what is unknown. It is very important to look at what is known and get levels of reassurance. But this is prevention, everybody knows this. In prevention, the bar for what is acceptable safety is so much lower based on efficacy. I always like to put in terms of absolute numbers, per thousand people, per 10,000 people, what is the upside, what are we preventing.

The things that strike me as the most important with influenza are preventing the hospitalizations due to influenza, preventing the deaths. Those are still in terms of numbers needed to treat below the one in a thousand category. Therefore, my sense is I at least want to

understand data that allow me to detect something on the off target effects that would be of comparable importance in one in a thousand.

So it is not just my concern about extrapolating hypersensitivity. It is extrapolating the entirety of the safety experience, and even for that matter understanding -- Dr. Gellin's points seem very insightful -- is this causal, is this a specific case of pleuropericarditis causal. We don't know. There are some things -- the temporal relationship, other factors could say yes, other factors would say no. Well, if you had more evidence here in terms of numbers of events for something like this, you are going to get a better sense of what is spurious and what is causal.

DR. STAPLETON: Thank you. I think we will break for lunch. We will have an opportunity to discuss this further when we go to the questions. We will reconvene at 1:30.

(The meeting recessed for lunch at 12:35 p.m., to reconvene at 1:28 p.m.)

A F T E R N O O N S E S S I O N (1:28 p.m.)

Agenda Item: Open Public Hearing

DR. STAPLETON: Next on the agenda is the open public hearing. I will read the announcement for open public hearings.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To insure such transparency in the open public hearing session of the Advisory Committee meeting, FDA believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product and if known, its direct competitors. For example, the financial information may include the company's or group's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

Should you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

We have three people who have requested. The first is Miss Barbara Lo Fisher, representing the National Vaccine Information Center.

MS. FISHER: My name is Barbara Lo Fisher. I am co-founder and President of the National Vaccine Information Center. I have no financial conflicts of interest.

It is understandable why both industry and public health agencies want to develop influenza vaccines that do not depend upon chicken eggs for production, expedited calculated and higher antigen yields as well as avoidance of egg allergy issues, and eliminating the need for preservatives or adjuvants are all worthy goals. I would like to commend Protein Sciences on the excellent methodology of these small clinical trials that included a head to head comparison with a true placebo, and then with another influenza vaccine with no potential confounding variables in terms of other vaccines given simultaneously.

I remember in 1995 when Swiss scientists found reverse transcriptase, which recopies RNA into DNA, in the live measles and mumps vaccines, as well as some influenza vaccines prepared in chicken embryo cells. Reverse transcriptase activity has been associated with the presence of retroviruses which can permanently alter the genes of the cells they impact.

I recall the CDC's explanation, which was that an

avian retrovirus integrated itself into the ancestors of the chickens which lay the eggs that were used to produce the chick embryo fibroblasts used for vaccine production.

In the current effort to fast track the use of a new technology which clones hemagglutinin genes from three influenza viruses which may be of human as well as mammal and bird origin and splice them into baculoviruses which are then used to infect caterpillar cells to produce the hemagglutinin contained in the new recombinant protein based influenza vaccine, there is always the possibility of advantageous agents contaminating insect cells could end up in the vaccines.

In fact, a 2005 World Health Organization document on regulation of candidate human vaccines state, "Most insect cells may have viruses in them, and infectious can be hard to detect and difficult to eliminate. Steps should be taken to eliminate them." This is something I found on the World Library on the Internet last night.

The inadvertent contamination of polio vaccines with SV40 serves as a cautionary tale. The public will clearly want reassurance that sufficient advantageous agent contamination screening is in place with this vaccine using an insect virus and insect cells for production, guaranteeing that no future unusual adverse events will be seen as more people receive the vaccine.

In addition, FluBlok contains three times as much protein as other influenza vaccines. There is always the potential for increased cross reactive autoimmune responses in individuals who are genetically predisposed to autoimmunity and immune mediated neurological dysfunction. I am thinking of the Bell's palsy case in these trials that may or may not have been triggered or exacerbated by vaccination.

The relatively small numbers of individuals in these clinical trials may not reveal the rarer but very serious complication involving demyelination of the brain and autoimmune disorders that have been reported following receipt of recombinant protein vaccines such as hepatitis B and HPV vaccines, including GBS, CMS vasculitis, rheumatoid arthritis, lupus and multiple sclerosis.

The new cell based technology is promising, but there are many unknowns. A larger pre-licensure clinical trial may answer outstanding questions about safety and efficacy and hopefully will include adults with chronic brain and immune system dysfunction, particularly those with autoimmune disorders, with a minimum one year follow-up period to determine if this vaccine exacerbates pre-existing chronic disease.

Thank you.

DR. STAPLETON: Thank you. Our second speaker is Professor Nicolai Petrovski.

DR. PETROVSKI: Thank you. I am the research director of an Australian company, Vaxine Proprietary Limited, that has been collaborating with Protein Sciences Corporation over the last three years. We don't have a financial relationship with Protein Sciences currently, but obviously there may be relationships of that nature in the future.

We have done research, both preclinical and clinical research, using Protein Sciences both seasonal and pandemic influenza antigens. We have compared these to a large number of commercial egg-based inactivated vaccines.

Our experience in testing these, as I say independently to Protein Sciences, is, we can't speak highly enough of the quality of Protein Sciences antigens. They are highly pure. They are just protein. They don't contain large amounts of contaminating RNA that we find in the egg-based vaccines.

But particularly, one of the committee members earlier asked about the experience of Protein Sciences in the pandemic swine flu area. In fact, our company did conduct independently of Protein Sciences a clinical study of Protein Sciences' H1N1 antigen earlier this year. I just wanted to take a couple of minutes to just give you an overview of our experience with that study, because I think it does address some of the questions that were asked by the committee.

The study was done with recombinant antigen provided by Protein Sciences. This antigen was produced extremely rapidly from the time of declaration of the pandemic, such that we were able to commence the trial in Adelaide in July of this year, in the same week that CSL, another Australian company, commenced a trail of an egg-based vaccine.

In essence, in terms of time lines, these were the first two trials in the world of both the traditional technology, the egg-based, and Protein Sciences' recombinant technology. So that highlights the fact that this technology can deliver in a very fast time frame antigens suitable for testing in the clinic.

I can't go into a lot of details about the outcome of that study. The publication hopefully will be available within the next few weeks. Just to give you an idea of the size of the study, it was in approximately 281 adults aging from 18 to 70. Over 50 percent of the people in the study had chronic disease, so this was a relatively high risk group.

If we go to the next slide, we tested a range of different antigens. Obviously at the time there was little known about what the necessary dose of antigen would be to generate sufficient immunogenicity to the novel H1N1 antigen, so we tested three different doses, three, 11 and 40

micrograms of Protein Sciences' recombinant antigen. At the same time, because our company has an interest in a polysaccharide adjuvant, we also tested the protein with the adjuvant.

Overall, the Protein Sciences antigen, as has been our experience with all the antigens they produce, was exceptionally well tolerated in the clinic. We didn't see any worrying side effects. Very similar to the data presented earlier for the seasonal antigen, essentially very mild pain was the most common solicited adverse event. There was nothing of any concern in terms of unsolicited adverse events.

The antigen was effective. It induced seroprotection in a majority of subjects. Obviously they were dose related seroprotection rates, so the highest seroprotection rate was at the highest dose of the antigen. There was also a very strong age effect, in that we had much higher rates of seroprotection in younger subjects, but in subjects over 50, just as we see with seasonal flu, there was a slightly lower rate of seroprotection.

So in summary, as I say, the experience with the pandemic is that Protein Sciences' technology really can deliver faster than any other technology antigen and vaccine that can be taken to the clinic in the event of a pandemic. The antigen being highly pure protein is in our experience

much better tolerated than the egg-based antigens, which do have as I say some contaminants, including RNA, which contribute to the low level of reactogenicity seen in those vaccines.

So as I say, we can only comment Protein Sciences on the quality of their recombinant protein. I personally believe this is the technology for the future when it comes to both seasonal and also pandemic influenza vaccines.

Thank you.

DR. STAPLETON: Thank you. The next person who requested to speak is Dr. Paul Mendelman.

DR. MENDELMAN: Thank you. Paul Mendelman. I am the Chief Medical Officer at LigoCyte Pharmaceuticals in Bozeman, Montana.

It has been an interesting two days. I ran the pneumococcal conjugate program at Merck for five years, and then did the phase III for FluMist, the live attenuated vaccine, for nine years, six years at Averon and three years at MedImmune. So I feel a little bit like Rodney Dangerfield.

Here are my comments and my questions. From what I just heard, I just want to make a couple of comments. From the time that MedImmune received the H1N1 swine flu strain until they developed the 6-2 construct using plasmid rescue, which is a validated licensed by the FDA, it was ten days.

Because people are looking at doses per egg, Medimmune gets up to 100 doses per egg with the live attenuated vaccine. MedImmune was the first one out the door in October with a commercial vaccine, at least as far west as California.

John showed some data for vaccine efficacy for LAIV, so let me just comment, not about adults. LAIV has higher vaccine efficacy against culture confirmed influenza, head to head, against the inactivated trivalent influenza vaccine in three studies, the only three studies that have ever been done. They are all reproducible and consistent, 2,000 children, 2,000 children, 8,000 children.

So that is my commercial, if you will. I have no ties with MedImmune, no ties with Merck, no ties with other than LigoCyte.

I may have missed a couple of things, but I want to make one comment about PSC01. I agree with the FDA presentation that the efficacy is 87 percent for the 135 microgram final formulation product. But it is not 68 percent by including the formulation that has got 15 micrograms of treating hemagglutinins and 45 micrograms of H3N2. That is not a final formulation, that is exploratory analyses. I think we all know what happens, when you put things together, it doesn't always happen the same.

What I may have missed is the lot to lot consistency data. Maybe it is in the briefing document, but

there is variability. You have got lots of numbers to look at between FluZone and Protein Sciences' construct. So did the lot to lot consistency for Protein Sciences pass all of the non-inferiority for licensure of this product with three consistent lots made consecutively? That is one question.

The PSC03 B strain, this is in the greater than 65-year-olds, where it didn't meet non-inferiority for the seroconversion rate, is B/Ohio and B/Malaysia the same lineage? If it is or it is not, for homologous antigens and reagents tested by Protein Sciences.

If you vaccinate someone with B/Ohio you test them with antigens from B/Ohio. If you vaccinate somebody with B/Malaysia, you test them with B/Malaysia. You can flip them back and forth if you want, if you think they are that dramatically different. But if we are making a statement that B/Ohio and B/Malaysia are that different, what is the data that shows that that is heterologous antibody production for HAI, what is the homologous antibody? Did it meet the non-inferiority criteria for the homologous strains for those two?

Then my last question is, given that microneutralization assays are much more sensitive than HAI, because you can neutralize the virus, I think we might get some light shed on HAIs, were microneut assays done in any of these studies, especially where non-inferiority was looked at

and not passed. Did they pass all the criteria looking at microneuts knowing that is not part of the FDA guidance or the standard, but it is a very sensitive and reproducible assay in research laboratories.

Thank you.

DR. STAPLETON: Thank you. Is there anyone else who would like to speak? If not, we will move on to the next item on the agenda. Dr. Pandey will present the questions.

Agenda Item: FDA Presentations of Questions

DR. PANDEY: Thank you, Dr. Stapleton. These are the questions for the committee this afternoon.

Do the available clinical data support effectiveness of FluBlok in the prevention of influenza disease caused by influenza subtypes A and type B included in the vaccine in adults A, 18 to 49 years of age, B, 50 to 64 years of age, C, 65 years and older.

The next question is, do the available safety data support the safety of FluBlok in adults 18 years and older?

The third question, is please comment on what additional studies, if any, should be requested postlicensure.

Thanks.

DR. STAPLETON: Thank you, Dr. Pandey. I think before we return to the first question, I would like to ask if anyone on the committee would like to have any further

general discussion or make any comments in regard to the questions.

DR. RENNELS: I have a comment that is directed to the FDA. Being a clinician, I don't understand why the primary end point is antigenically matched influenza. Isn't really the clinically important parameter prevention of influenza regardless of whether it is matched or not?

Having said that, most of the studies of this vaccine, the efficacy looks pretty good, particularly given that it was so poorly antigenically matched.

DR. STAPLETON: I don't know if other people would like to comment. I might comment on that from my perspective and experience. If you are trying to look at efficacy of a drug that is against a disease other than you are studying, you can't really expect to see any effect. So I think my take is, it is appropriate to look at only matched strains. I don't know if epidemiologists would like to comment otherwise.

DR. EICKHOFF: I would disagree a little bit, Jack. I think antigenic drift from year to year is a fact of life when you deal with influenza. The key end point should be prevention of influenza, not matched or mismatched.

DR. STAPLETON: I don't agree. I don't disagree with the clinical outcome, but I think you can't expect a mismatched vaccine to work very much.

DR. EICKHOFF: Well, they do work, but not as well as if they were matched.

DR. STAPLETON: Sure.

DR. FLEMING: That is a great point. It is a great discussion. I think the rationale that you have given is the one that is recognized by all. That is, if you are developing a vaccine and you are expecting, due to the nature of the immune response, that you will be particularly effective against circulating strains that match with your vaccine, you will enhance the sensitivity of the assessment.

But I agree with my colleagues. I think it comes at the expense of some true clinical relevance. You are vaccinating a population to try to provide favorable benefit to risk. That benefits very significantly the hospitalizations, the major events, the deaths, but also to the overall burden to society from the influenza. It can be misleading, in the sense that you can compare two vaccines that have a similar level of matched CDC ILI efficacy, but one has a broader spectrum that truly is going to be more effective.

I always wonder -- I don't know about this, but I always wonder about opportunistic aspects and off-target effects and what you are seeing, you are assuming, when you look at cause specific. When you look at cause specific, you are assuming you are neutral on what you are not targeting.

If this vaccine were neutral on what it is not targeting, it would have been dead in the water in this case, because there were no events. There were five to eight events on what they were targeting.

So you are throwing away the dominant prevalent circulating strains. Of course, then the issue is, how do we interpret that. I guess my sense is that everything is relative, so a lower limit of vaccine efficacy of 18 percent in the context of other available interventions, I worry about its impressiveness and I worry that it wasn't the primary or secondary analysis. But I wish it had been.

I agree with you. I don't mind looking at secondary supportive analyses that are more sensitive that look at cause specific, but ultimately it is what is the net effect, because that is what the patient cares about, is ultimately what is the burden of disease to their overall quality of life and their morbidity and mortality. I tend to prefer to have the most clinically relevant measure to patients as the dominant safety measure.

DR. DEBOLD: I understand that, but it seems to me if I were a manufacturer trying to make vaccine like this, to some extent it seems that it is unfair, because while they can produce a product that produces titers, that does what it is supposed to do, to some extent they are hamstrung by the fact that this committee recommended putting one, two, three

strains in there, and the strains don't end up matching what circulates. So is that there? That is not really fair to them, it seems to me.

DR. LEVANDOWSKI: I will just come back to what I said before. There is a little bit of arbitrariness in determining what is matched and what isn't. It is not just, this is it. We don't actually know. As an RNA virus, influenza is mutating continuously, so it is always throwing off variants. As others have pointed out, that is a fact of life with influenza.

I don't think you have to blame the committee either for choosing particular strains, because the committee doesn't have any control over what is happening out there in nature. To some extent, we don't even understand how the variability of the hemagglutinin goes on.

A little bit puzzling this year is that the 2009 H1N1 seems to have a lot more antigenic consistency as time has been going on. Maybe that is just because of the newness. I don't think we understand that. I think it is something for a lot of research.

But again, it is this arbitrariness as to what is matched and what isn't. I think I would agree that it would be fairer to consider everything. I know the primary end point that was chosen might be antigenically matched. There is a definition for that that was followed here, but maybe

that was a mistake in some sense, not that we should go back and redo the data, but it is a bit of a puzzle to have to deal with.

DR. STAPLETON: I don't mean to sound as though antigenically mismatched doesn't mean there might not be some cross neutralization. I think with the B strains in that season, about 80 percent were in the other lineage.

DR. LEVANDOWSKI: Let me comment on that also. In immunologically primed individuals, it is not that there is totally no effect of the mismatched vaccine. There is some cross reactive antibody that is produced. In every study that you look at, you see that that is true. Even if it is lineage A versus lineage B, provided both influenza B viruses, for people who are immunologically primed with the first one, you give them the second one, and they get some boost on the antibody to the first one. That is highly variable, however. In some instances it is really a tiny amount, but it is not nothing usually.

DR. STAPLETON: I think the power of the study to see those differences from that cross reactivity would be impossible.

DR. MC INNES: I have two issues that are causing me to think a little bit about the relative importance of seroconversion with seroprotection when the baseline titers are already high, and how to think about the B data,

particularly in the context of older individuals, where the associated morbidity is usually not particularly meaningful. I am just wondering what people are thinking about that.

DR. SUN: I just wanted to address a question that was addressed to the FDA. I want to comment briefly about that, why the approach of looking at matched strains.

I think that is a situation where it is an optimal situation which we ideally would like to see. That would show us probably the most robust kinds of data if it turns out that way. But I think we all know that influenza is very unpredictable, even though the primary end points for looking at matched strains very well could be, the reality didn't cooperate and we get unmatched strains. So that is a less optimal situation.

That said, I think we also have to realize that we actually license vaccines, influenza vaccines, without clinical culture confirmation studies. We have been doing under accelerated, but we are using immunogenicity as end points that are likely to predict clinical benefit.

So I just want to put that in context.

DR. ROMERO: To follow up on Dr. McInnes' comment, and at the risk of being corrected by Dr. Eickhoff, I think you are correct, the bulk of disease that we see due to B is in childhood, young infants. I like you have been thinking about that from that perspective.

If this was a vaccine that was going to go into kids, I would be very nervous about going anywhere with it. Older individuals don't seem to have -- because probably being exposed to this virus over time, don't have as much problem with it. I'm not saying it is not important, but it is not going to be the population that you are worry about getting infected with B.

DR. EICKHOFF: I would just add to that, as an adult infectious disease physician I wouldn't mind if there were no vaccine at all. The pediatricians would raise bloody hell.

DR. GELLIN: Since you brought this up about past decisions by this committee, I recall in the pre-H1N1 era, which wasn't that long ago, but seems like it was a long time ago, we had this discussion at a table like this about a tetravalent product that would look at two B strains, particularly with kids in mind.

So I'm glad Pamela raised that. I think if I understood, Pamela, your intention was to think through how we would weight that data differently than we would weight the A data.

Agenda Item: Committee Discussion and Recommendations

DR. STAPLETON: That was only February. Dr. Debold has the luxury of not having been on the panel the year we

had to pick that strain. Are there any other comments before we go to the specific questions?

The first question then is, do the available clinical data support effectiveness of FluBlok in prevention of influenza disease caused by influenza subtypes A and type B included in the vaccine in adults -- and there are three questions -- A is in the 18 to 49 years of age population. Comments, discussion?

DR. FLEMING: Just to come back to this B issue, which is part of what is my concern. What you are saying, Ted, is in a pediatric setting it would matter, in an adult setting it matters less. If it matters less though, at least one shouldn't be claiming, shouldn't be adding to the claim if there is evidence for B effects that you have the effects. You are just saying you would be accepting of one that didn't have the effects.

DR. EICKHOFF: I think what you are saying is generally true, and I agree with it. The morbidity burden from sero group B influenza is there, but it doesn't kill adults, particularly the elderly. So we basically know the mortality burden.

DR. FLEMING: Not true for children. And that is important, although it comes back to what we are trying to achieve, and that is certainly an important part of what we are trying to achieve with the vaccine. But we are also more

globally looking at public health burden that would include hospitalizations, would include loss of work time and other health incremental effects of influenza.

So while it is really important knowing what the mortality risk is induced by, there are more global burdens induced by influenza.

DR. EICKHOFF: True.

DR. FLEMING: Coming back to this discussion, my own sense is that if I were designing a trial, I would be inclusive in terms of what matters most to patients. Then I would look at the cause specific as supportive evidence. By the way, if I were doing it solely to approval, which is an interesting separate discussion I don't want to get into, but that doesn't eliminate the need to still do efficacy. Approval is a conditional approval; you still have to do a proper validation that would prove efficacy.

But coming back to this point, it is not a trivial issue scientifically when we use statistics to use them properly. By no means are they the essence. They are a tool that we use as assistance. We use estimates, we use P values for inference for these confidence intervals.

It is more inherently problematic to interpret data when you are clearly specifying a primary analysis and the trial clearly fails, not because it established evidence against what you were trying to show, it just didn't give you

evidence. Then the secondary had the same thing. Then you get to exploratory analyses. So it comes down to interpreting the strength of evidence even in the only setting where there is direct evidence, and that is 18 to 49-year-olds.

The trial was designed for an estimate of a 70 percent vaccine efficacy, ruling out 40. The estimate is more in the range of what you wanted to rule out, with lower limits that are down toward 18 percent. That 18 percent is not a rigorous lower limit, because it is from an exploratory analysis. There are things called regression to the mean bias, random bias, et cetera, when you fall back on other hypotheses, even if they are ones that some of us would have said should have been the primary. They weren't.

So it is difficult to sort out how to address that. It is difficult to sort out how to address the informative missingness, when there are three times as many missing people as there are events. Those are all issues that make it difficult. It is difficult when you already have alternatives that are effective.

Ultimately we are going to discuss safety in a bit. My answer to safety is influenced by how compelling efficacy is. But I can't help to also answer the efficacy question based on what is known about safety. As you probably know, my reasoning is similar to Dr. Fisher's in the open public

hearing. That is, what we see in safety is reassuring, but there are some potential signals with the size of the trial here that is not going to give us a reliable answer.

So I am jumping ahead to safety and I want to stay on efficacy, but what you have to see in efficacy is greater when there are uncertainties in safety. Just as what you have to know about safety is more reliable when there are uncertainties about efficacy.

So to me it is complicated by all of these issues.

DR. STAPLETON: Other comments? Then we need to vote on the question of, do the clinical data support effectiveness in the 18 to 49 year age group. For those of you who weren't here yesterday, we now vote with our microphone. There is a button that you push, and then it will be tabulated.

(Whereupon, the committee cast their votes.)

MS. WALSH: Total votes today will be 11 voting members. Dr. Rennels will be a nonvoting member. For question 1A there were nine yes, zero abstain, two no. Of the 11 voting members, there were nine yes. The two no votes were Dr. Debold and Dr. Fleming.

DR. STAPLETON: The next question is, do the available clinical data support the effectiveness of FluBlok in the 50 to 64 years of age for the prevention of influenza disease caused by subtypes A and B.

(Whereupon, the committee cast their votes.)

MS. WALSH: For question 1B, of 11 total votes, five were yes, zero abstain, six were no. Of the 11 votes, Dr. Stapleton voted yes. Dr. Gellin voted no. Dr. Romero is no. Dr. DeStefano is yes. Dr. Eickhoff is no. Dr. McInnes is yes. Dr. Wharton is yes. Dr. Sanchez, yes. Dr. Levandowski, no. Dr. Fleming, no. Dr. Debold, no.

DR. STAPLETON: Thank you. For the final question of this aspect of this question, do the available clinical data support the effectiveness of FluBlok for the prevention of influenza disease caused by subtypes A and B included in the vaccine in adults aged 65 and older. Please vote.

(Whereupon, the committee cast their votes.)

MS. WALSH: For a total of 11 votes, there were two yes, zero abstain, nine no. Of the 11 votes, the two yeses were Dr. Wharton and Dr. Sanchez.

DR. STAPLETON: The second question for the committee, do the available safety data support the safety of FluBlok in adults 18 years and older? The topic is open for discussion.

DR. GELLIN: In the presentations we heard a lot about the back and forth between FDA and the sponsor. There was another discussion, my term du jour is Tom's informative missingness. So I am assuming that those lost to followup, you got the FBI to try to find these people, to find out

whether or not you could find them and put them into a data set.

Maybe that is it. I don't know if there is additional data that might get scared off. I know this is not simple to do and it is a long time ago, but particularly this question about the pericarditis and what we know about that evaluation, and whether or not that could be looked at again. I think that knowing an etiology to that case would have a huge impact on my assessment of this one. Otherwise we are left in this limbo land of not knowing whether or not it could or couldn't be related to the vaccine.

DR. DEBOLD: I have got concerns too about the Bell's palsy and the woman who had the hypersensitivity and the swelling and what have you. I realized that in both of these situations there was a prior history of issues with them. But if the vaccine has the potential to exacerbate existing illness, I think that matters. I think that is something we have to understand, because it may end up being something that that is a contraindication for some people.

So I think the hypersensitivity, there seemed to be a trend toward more hypersensitivity issues in the experimental group.

DR. LEVANDOWSKI: Something that hasn't come up, or I missed it if I did, repeat dosing in people. This is the kind of vaccine that is going to be used yearly. I didn't

hear any data, or I don't know if any data exists about repeated dosing, and more particularly what effect that might have on sensitization.

Taking that one step further, whether any of the reactions that were identified, even if they were considered to be related or not related possibly or probably, whether any of those might represent what might be considered related.

It was mentioned earlier today that we probably ingest a lot of baculovirus and related compounds in our food. Is it possible that someone could be sensitized, or is there evidence counter to sensitization that would result in something else in the environment causing a reaction that might be delayed by ten days or two weeks or three weeks.

DR. COX: I would like to make another comment. I am dumbfounded by the previous votes of the committee. In principle efficacy studies are only allowed in individuals 18 to 49 years of age. Beyond that age group you are forced to do immunogenicity comparison studies. So if the committee here today says that all the other vaccines also don't meet the criteria and are non-effective, then I can understand the vote. But otherwise I am really lost.

DR. STAPLETON: I think we were answering the question to our best ability, so thank you for your comment. Any other comments?

DR. FLEMING: Just to add to what has been already commented about. My sense is that the frequently occurring safety risk profile looks encouraging, particularly injection site reactions and other common events. But as has already been noted, as was reflected by the answer to the first question, the efficacy issues are a mixed sense, and there are other vaccines that are available, so the bar in terms of safety is not as high as it would be if we had more compelling evidence of efficacy.

The level of the safety bar is influenced also by how widely used an intervention is. Sometimes out of some sense of necessity one proceeds with less than what one would reliably want to know for benefit to risk for the overall safety profile.

But we are seeing more and more recognition across areas in the regulatory world, in the scientific community, that in these widespread indications, it really is of compelling importance to public health to understand adequately, reliably, both efficacy and safety. We have seen a complete paradigm shift in the last 18 months at FDA in type two diabetes drugs, in part because they are so widely used that six-month hemoglobin A1C results are not sufficient.

We really need to understand that for every type two diabetes drug, whether there is a cardiovascular signal or not, there now needs to be a large scale long term trial

to understand the safety as well as the efficacy. COX-2 inhibitors are agents that provide benefit, but the off-target effects that are rare but are profound need to be understood. There is a 20,000-person trial ongoing right now to understand more effectively what that safety profile is.

So it is not my sense that there is a proven negative effect on a major morbidity or mortality end point that would trump the benefit. But it is my sense that there is a sufficient signal and an inadequacy of understanding that, if I go back to Dr. Fisher's comments in the open session, with rare but serious complications that can't be ruled out by the sample sizes that we have, it seems important for an agent that can be used so widely to have that adequate understanding.

So my sense is, the way forward here should be an evaluation of safety risks that allow us to better understand these rare but what could be important events that would alter benefit to risk, and that also gives us a broader sense about the entire range of the label. If the interest is beyond 49-year-olds, then we really want to have a more enhanced understanding across that age spectrum.

DR. DeSTEFANO: We face this with most vaccines. At the time they get licensed, the preclinical licensure trials have not been adequate to fully evaluate the long term safety in particularly rare events. We face that with every

vaccine. So what you evaluate is the reactogenicity.

I am pretty comfortable here that this vaccine has the same reactogenicity profile as Fluzone, which was the main comparitor. Fluzone and seasonal influenza vaccines have a proven track record of being extremely safe over many years, with postlicensure studies and large database studies.

One case of pleuropericarditis is one case. Unless there is a specific biological mechanism or biological marker that could indicate that that was caused by the vaccine, or you couldn't rule it out, or you could identify some other cause, but right now it is very difficult to evaluate.

So I think the reactogenicity appears to be similar to the Fluzone, and I think this question three will become critical when we begin to use this vaccine on a large scale.

DR. MC INNES: I think the reason we are stuttering so much is that the database isn't very large. I give enormous credit to the company and the investigators who have clearly done so very nice work and a lot of care and attention, and there has been a huge amount of progress made.

But I would like to see larger databases on safety. I look back on other novel influenza vaccines that were licensed in the last decade. A very compelling question was, what about annual re-immunization using the same thing? Once this is licensed and it is out, that is what we are looking at. We are looking at an annual vaccination, and I think we

need to have data of that nature provided.

I also think that it would be very wise to nest these studies in clinical sites, where follow-up of subjects is of the highest importance. There is not a signal in my mind that I am saying, whoa, I am really worried; I'm not. But there is missing information, and that is concerning in the earliest stages of development of a product.

I think if adequate attention was paid and additional data were generated including efficacy and immunogenicity data, I think it is entirely feasible that a really good body of robust data will be there to support the vaccine. I am not comfortable particularly with the size of the safety database at this point.

DR. EICKHOFF: In her discussion right after lunch, Dr. Nolletti was I thought a little bit dismissive of the issue of hypersensitivity phenomena in the elderly population.

My immunologists back in my home shop tell me they see a lot of hypersensitivity phenomena, increasing as the patients grow older. I have had some of these myself.

That said, is there some reason that question number two covers the entire population 18 up to over 65, rather than being broken down into the three relevant age groups?

DR. STAPLETON: I would interpret this to mean in

all age groups, but I would ask FDA. Dr. Baylor is nodding his head yes.

DR. DEBOLD: Are we also supposed to interpret this as being for all people, not just healthy subjects that were recruited, but everybody regardless of health status?

DR. STAPLETON: My interpretation again is, like the seasonal flu vaccine, it would not be restricted to healthy people, but we don't have the data to know the immunogenicity and safety.

DR. ADAMS: Vis-a-vis the missing people, unlike when we talk about dropouts, that is more of a drug thing, in flu you get a single dose, you come back 28 days later, you get a blood draw. If you go from the single dose to the blood draw 28 days later, there were virtually no dropouts. In the flu business we say lost to follow-up.

So what happened was, people -- it is not like they are continuing to be on a drug every two weeks, and all of a sudden the side effects take over, and people say I am out of here, and I drop out. That is not the case with flu; people came back for their blood draw in 28 days.

Now you have weekly phone calls. What happens is, if you can't reach somebody three times, you are considered lost to follow-up. So they put them in a dropout category.

I can say that virtually all of the people lost to follow-up came from four sites. One to two percent lost to

follow-up in 20 of the 24 sites. It is not because of side effects, because as you all know, after 28 days when you get a flu vaccine, we only then monitor SAEs; we don't even monitor AEs in accordance with the FDA guidance after 28 days.

So I wanted to put that in perspective. It should be a little helpful, I think.

DR. STAPLETON: Dr. Treanor, did you want to make a comment?

DR. TREANOR: This is from a long time ago, but just to remind you that there is some experience with two-dose schedules of baculovirus expressed hemagglutinin, which were done in the context of studies of H5 vaccine.

Then there is with Protein Sciences vaccines generally an experience with multiple dose schedules for other antigens as well, none of which have suggested that there is sensitization or an increase in side effects with multiple dosing, although the total number of subjects is relatively small.

DR. STAPLETON: Are there any additional comments or discussion on this topic?

DR. GELLIN: To build on Frank DeStefano's comments, I did find particularly helpful the cross comparison of reactogenicity of this product, Fluzone and placebo. I think in many ways it is telling about society

when you see that one in five people if asked several days after some thing. But to have those things together was particularly helpful, particularly as we are discussing in the H1N1 context about the H1N1 vaccine and its similarity to -- and its reactogenicity to seasonal vaccine.

To have this kind of data available I think is very helpful, so I am glad the company put the effort in to do those three.

DR. WHARTON: I am sitting here, looking at this question and struggling with it in terms of answering this as a yes, no, abstain question. There is the issue of hypersensitivity that the studies present that I would like to understand more about. There is the issue of the dropout rate from the large trial.

The available data do support safety. The question is what is not available. So in looking at this question, this is kind of hard to answer.

DR. BAYLOR: What I think the question is, as you have interpret the available data, question three or the discussion will get you there for the other. So I would recognize answering the question as it is written, but number three will get you to the other point if there are recommendations to be made.

DR. FLEMING: Just from a regulatory and legislative perspective here, this is asking our advice,

whether the available data support the safety. So one has to establish well controlled trials in efficacy and safety.

If the data are favorable and are persuasive relative to what one needs to know about safety, then it seems to be the answer is yes. If the available data partially answer the question, but in the context of what is known about efficacy, what needs to be known about safety extends beyond what the available data indicate. My sense from the regulatory perspective, the answer is no. So this is not saying -- because again, that gets down to the classical absence of evidence is evidence of absence. The best thing to do then is to get minimal evidence, such that what you have doesn't create a bad signal. That is completely inadequate from a regulatory perspective.

The question is, at least what I would hope we are being asked, is, are the safety data sufficient in the context of the nature of efficacy to be able to reliably answer the question that this product has a beneficial benefit to risk profile, which means we have understand safety adequately to answer that question.

DR. STAPLETON: Very rarely do we have large enough initial trials to pick up all signals. It is very rare, I think. So I think that we have to base it on the numbers we have, which are not as high as we would like, but we always want bigger populations.

DR. FLEMING: Although that would suggest that we are always dissatisfied. Sure, we always want more, but we are not always dissatisfied. If there is a strong efficacy signal, and there isn't a basis for having an offsetting concern about safety and what is there provides a sufficient basis to conclude that safety will be favorable relative to what we know about efficacy, then approval would be appropriate. In that context you still may explore certain other elements in a postmarketing setting.

DR. STAPLETON: I have tried not to put out my views too much, but I guess based on one case of pleuropericarditis and one hypersensitivity out of the 4500 people, I think that meets my criteria.

DR. DEBOLD: I am looking at slide 61 from the FDA and trying to make sense of it. In addition to the one pleuropericarditis, there were four reports of hypersensitivity in the experimental group, one in the placebo, zero in Fluzone, one report of urticaria in the experimental group, zero in placebo, zero in Fluzone, nine reports of rash in the experimental group, three in placebo, six in FluBlok, and one with swelling of the face, and there were a few other things.

So to me, these data are not equivalent across these groups.

DR. STAPLETON: I interpreted those data on the

rash as, the rate is higher for Fluzone, .8 as opposed to .3.

DR. FLEMING: The control rate, I would call it a wash on rash. It is the non-rash events that are -- when you add the placebos and the Fluzone, that is a comparable number to the FluBlok. So the rashes are nine-nine, but the other events are seven to one.

DR. STAPLETON: Something we need to discuss in the next question is, pleuropericarditis is an autoimmune phenomenon which needs to be assessed, I think. Any other discussion or comments?

DR. NOLLETTI: I can give you a little more detail about the hypersensitivity, the four hypersensitivity events.

There was one urticaria. That was mild, occurring four days post vaccination, and the subject also had symptoms of sinus infection. There was the case of the swelling of the lips and tongue. There was a case of pleuritis, dizziness, some facial swelling that was characterized as being mild that occurred in a woman 16 days post vaccination. She had a puffy upper lip, puffy eyes. She also had a history of being ectopic.

Then there were two cases of seasonal allergies or infection related rhinitis that weren't temporally related to vaccination. They appeared unrelated, but were coded hypersensitivity.

DR. STAPLETON: Thank you, Dr. Nolletti. Any other comments or questions? If not, then we shall vote on the question, that reads, do the available safety data support the safety of FluBlok in adults 18 years and older.

(Whereupon, the committee cast their votes.)

MS. WALSH: Total of 11 votes. There were five yes, zero abstain, six no. Dr. McInnes is no. Dr. Wharton, yes. Dr. Sanchez, yes. Dr. Levandowski, no. Dr. Fleming, no. Dr. Debold, no. Dr. Stapleton, yes. Dr. Gellin, no. Dr. Romero, no. Dr. DeStefano, yes. Dr. Eickhoff, yes.

DR. STAPLETON: Thank you. I will go to the third and final question for the committee. Please comment on what additional studies if any should be requested postlicensure. This question is open for discussion.

DR. EICKHOFF: I'm sure others will come to my mind as we go along, but the first two are a better safety database in the elderly population, 65 years and older, which I think standing by itself is pretty inadequate at the moment, even though I was one of the ones that voted yes.

Two, I think it was Roland who brought up the issue of repeat annual re-vaccinations. This should be looked at very closely, particularly with an eye to increasing the risk of hypersensitivity reactions in any age group. I'm sure there will be others.

DR. DeSTEFANO: I think a large postmarketing phase

IV study is called for in this case, given that this is a new vaccine that in essence has mainly been evaluated for reactogenicity now. I think the study should be done to screen for all medically attended adverse events with a possibility of follow-up and to confirmatory studies of any signals that may arise.

DR. STAPLETON: I have a list of special populations which I'm sure we are all thinking about. Included in addition to the elderly are pediatrics, pregnant women, immunosuppressed patients, and particularly paying attention to vasculitis and autoimmune diseases.

DR. FLEMING: I think we need to understand safety better, and I also think we need to understand efficacy better. How broad a population depends on what the label is. If the label includes elderly, then we need a much more reliable assessment.

If I can refer to Dr. Fisher in the open public hearing one more time, I actually have her perspective as well. I think we need a larger pre-licensing study. But whether it is pre-licensing or post-licensing, it should be a study of sufficient size that we can more reliably understand benefit to risk where that can be influenced by what I would call a signal, by no means established, but a signal for off-target effects here that could really influence benefit to risk.

My sense is, that is a study that would be several fold larger than what we currently have. A study of similar size to what we currently have in the 18 to 49-year-olds, but a parallel size in the 50 to 65-year-olds, and parallel size in the over 65-year-olds would be the lower limit, but it would give us at least a sense of detecting one in a thousand events, getting more insight about these hypersensitivity reactions and other factors that could be there in real for which there are already some signal, but then there are other things that we readily may not have detected as yet, particularly in the people over age of 50.

By the way, a placebo controlled assessment has certain advantages, and it is achievable, at least in a premarketing setting, in people below the age of 50. But either in a pre- or postmarketing setting, an active control trial would be very appropriate and very informative.

In fact, if this vaccine is through its construction thought to potentially move us forward, it would be reasonable to consider a superiority trial against an active control. You are not ruling out a lower limit of 40, you are just ruling out quality.

So there are a number of things that could be considered that would allow us to move forward and get much more insight, either pre- or postmarketing, into what the true efficacy actually is in a broader set by age, and what

the safety profile truly, more reliably is.

DR. EICKHOFF: This is really not a specific point under question three, but rather a generic comment. I find myself, and I suspect many of us also, quite ambivalent about this vaccine, partly because what we are dealing with at rock bottom is a pretty mediocre vaccine. I include not just the manufacturers of this vaccine, but trivalent influenza vaccines in general. This product fits right in.

The huge advantage of this product, and I mean huge, is that they can produce a vaccine quicker than the TIV manufacturers. Make no mistake, I think that is a major advantage, and it is a breakthrough in many ways for the United States to have available a vaccine made in this way, with recombinant hemagglutinin. It would certainly have been helpful to have this available this fall, make no mistake about that.

DR. DEBOLD: To add to the special populations anyone with immune mediated illness, not just the autoimmune illness, but particularly asthma reactive airway, hyperimmune illnesses of any sort.

DR. STAPLETON: Are there any other comments or questions? I think we are waiting for the consultation to finish here to see if Dr. Baylor has a comment or question.

DR. BAYLOR: Perhaps we can get a little more discussion on the safety. In looking at the vote on the

efficacy on the age groups, perhaps we can get some more discussion, not a vote, a discussion on the safety in the 18 to 49-year-olds.

DR. STAPLETON: The question was over 18. Is that part of the issue?

DR. BAYLOR: In question two it was 18 and above.

DR. STAPLETON: You said 18-49. Are you talking about the efficacy or the safety?

DR. BAYLOR: No, in safety we said 18 and above. The way the vote broke out on the efficacy, where we divided it among the three groups, I would like to get some more discussion, not a vote, but discussion on that data set for the 18 to 49-year-olds, on the safety.

You commented overall on safety. Now, based on the vote that we voted in question 1A, could I get some comments and discussion on the safety data in the 18 to 49-year-olds, not a vote, but a discussion. Or if the comments you made for question two, you really do feel that those comments apply across the board from 18 and above, then I would like to hear that as well and just reiterate that.

DR. STAPLETON: I'll start and pass it around the table. I feel that the safety data do not raise significant red flags, except they raise a few points that need to be carefully examined in postmarketing.

I think the reason I was more comfortable in 18 to

49 and 50 to 64 is the limited amount of data in the older group. That was my biggest concern.

Dr. McInnes, you look like you are thinking about saying something.

DR. MC INNES: My problem with this is that in the PSC04 study, that we have the lost to follow-up cases. I am conscious of this vaccine being a new vaccine. This is a new vaccine. This is not a strain change. The burden to me is higher.

I reiterate, I don't feel the safety database is large enough for me to be confident that my answer is grounded in data. So in addition I want to see repeated vaccination. I would like to see a lot more data supporting how this vaccine will be used in the end. It will probably be fine, but I would like the data to show that.

So if I am asked to go 18 to 49, I still don't believe the safety database is adequate.

DR. STAPLETON: I have a question for Protein Sciences. What was the lost to follow-up at day 28, so that you have 28 days of follow-up safety data?

DR. COX: .5 percent in each group. In placebo there was no difference between the two groups.

DR. STAPLETON: So the roughly nine percent were lost after day 28, which was the phone follow-up?

DR. COX: During the phone calls.

DR. MC INNES: I have a question back to your slide 38, where you have a statement that says nine subjects withdrew as a consequence of AEs, five FluBlok, four placebos, seven due to pregnancy. It was on this particular point that I asked for specific follow-up information, and I haven't heard reassuring information about this.

DR. PATRIARCH: Hi, I am Peter Patriarch. I am a consultant to Protein Sciences. Pam, I'm not sure that we can completely answer that. I would have to look up the study report. But basically the group of patients that was mentioned in that slide were people who specifically withdrew because of some adverse event.

So to state it another way, to try to get at your question, there were quite a few people as you saw who were lost to follow-up during the course of the study, about three and a half by day 28. Some of those people could have withdrawn as a consequence of side effects, but we don't know that. So we just don't have that information. While the remainder then dropped out as a consequence of not being able to be contacted during the flu season.

Everybody was telephoned every week throughout the flu season. Once you missed three phone calls, you were considered lost to follow-up, and no further efforts were made. During that time though, there were considerable efforts to re-contact each person. There are only so many

times you can call these people. There are only so many certified letters you can send.

Part of this, as Dan explained before, was related to where these study sites were. Some of them, for example, New Orleans, Los Angeles, were predominantly inner city clinics. They had difficult patient populations to be able to follow up.

So part of the reason why there was so much loss to follow-up had to do with the milieu of the patient population. Could that have been better? Of course, it could. But the concept that a lot of those people dropped out of the study as a consequence of adverse events, that just doesn't seem right. If you look at the known adverse event profile and the fact that they only got one dose, it is not as though you were in a drug study where they have to take drug every day for X number of weeks and months and so on and so on.

So I guess our interpretation of that as being a significant factor, we just don't see that. That is our interpretation.

DR. MC INNES: But you can't refuse it, either.

DR. PATRIARCH: That is correct.

DR. MC INNES: I think while we always have the challenge of reaching out to populations to have good ethnic and racial distribution and consequently it makes a trial

sometimes more challenging, that becomes more statistically meaningful when you have a smaller data set to look at. If there were a much larger data set, I might not be asking such specific questions.

DR. NOLLETTI: I'm not sure if this is helpful, but if you look at my slide 103 as a backup slide, these are discontinuations due to adverse events. In the footnotes, for study PSC01 and PSC06, there were no discontinuations due to AEs, and for PSC03 there was one Fluzone recipient who discontinued due to cerebral hemorrhage. For PSC04 in the table, in the FluBlok group I found six discontinuations due to AEs. One was a pulmonary embolism and death, one was the pleuropericardial effusion, one was the case of pregnancy miscarriage, and then there were three more pregnancies. In the placebo group there was the motor vehicle accident death, a second case of multiple fractures, and two pregnancies.

Then in slide 100, slide 100 is pregnancy outcomes. In the FluBlok women, complicating AEs included hyperemesis, pulmonary embolism, a staph infection and miscarriage. Amongst the Fluzone recipients, complications of AEs included kidney stones, appendicitis, hypertension, ectopic pregnancy and miscarriage.

DR. FLEMING: Just on that point, it is not clear how comprehensive this table is when you listed discontinuations due to AEs. Discontinuation of what? That

term is often used in a vague way.

DR. NOLLETTI: From the studies?

DR. STAPLETON: These were the withdrawn subjects, is that correct?

DR. FLEMING: The point is, they are not discontinuing from further intervention. They are reporting that they don't wish to be followed specifically because of their AE, that is what you're saying?

DR. NOLLETTI: That was my understanding, yes.

DR. FLEMING: But what is unclear is how many people discontinued in ways that could have been influenced by AEs. But the people who discontinue aren't like the people who don't. It is somewhat reassuring to know that with this 12-plus percent missing data, that at day 28 the missingness rate was certainly a lot lower. But that is still 162 people, when there were only 122 events. Those 162 people are going to be different.

It will be useful though for the FDA to really probe -- you will have more time to do this than we will be able to discuss today -- to get the best insight you can. But missingness is rarely pseudo random. Happening in a comparable number of people across the two arms is only very slightly reassuring that it is not going to be biasing the overall difference.

DR. STAPLETON: Other comments? Dr. McInnes and I

weighed in. Anyone else like to weigh in on question 1A?

DR. FLEMING: I guess I will weigh in on it. My own sense is, my concern is greater about what we don't know about safety in those people who are above age 50. I have a greater concern there. But it is not a non-concern in the 18 to 48-year-olds.

For me again, I apologize for repeating, but it is always benefit to risk. The nature of the evidence for efficacy is not strong. I think it is certainly suggestive that there is some efficacy, but it is not strong and clear in terms of the magnitude. The issue of missingness is one aspect.

Repeated vaccine issues have been mentioned, but in essence, the lower limit of the confidence interval is around 18 percent on an exploratory end point. That is our understanding of efficacy, and that is influenced by missingness.

So when I get to safety, it is important to be able to reliably understand whether safety is sufficiently favorable that it wouldn't offset the nature of that efficacy signal. So while I have more information there, it would have been really extremely helpful to have had the additional information from the older ages, if not also greater numbers from the 18 to 49-year-olds, to get a sense about whether or not the hypersensitivity reactions, et cetera, are real.

So I have concerns about safety in the 18 to 49-year-olds, but it is a greater concern because of even less evidence in the people who are over 49.

DR. STAPLETON: Dr. Eickhoff, do you care to weigh in?

DR. EICKHOFF: I was one of those that voted yes on question number two, anyway. But I share Tom's concern. I am sufficiently content with the safety database in the 18 to 49, but it is very weak in the older 50 to 64 and 65-plus.

DR. DeSTEFANO: I have similar feelings.

DR. ROMERO: Again, I think the data is weak. The problem is that this is a new vaccine, and it is a new technology, it is a new way of doing it, relatively new; there is another vaccine.

I think one of our jobs is to insure the public safety. If the data is not robust enough for at least me to feel that all the questions have been answered, then I have to vote based on that information.

What I have here is data. There are some weaknesses. I think the vaccine is probably going to be okay, but the data that was presented for analysis today is not the type of data that I need to make a really informed conscientious decision. That is the problem, because you need more data. There are holes in the data. This can be remedied very quickly in the future. The vaccine is a great

technology. It just needs to be advanced and presented in a better form.

DR. GELLIN: I want to build on Dr. Eickhoff's comment before about this technology and how important it is to have this kind of technology, particularly when you think about how nimble we will need to move to have a vaccine against something that emerges and have something relatively quickly.

This is going to be the first of several technologies that we are going to be faced with. While this is an application for seasonal flu, and there are lots of people who get seasonal flu vaccines, you also have to think about the potential implications for broad scale mass vaccinations. I think that again highlights the importance of having as robust a safety database as you can before you would want to make a recommendation for a product like this to be given to tens of millions of people.

So I think in many ways we are fortunate to have this conversation now. I think it is going to be a prelude to other conversations as we see other interesting and important technologies that move us along. Speed is really important. We deal with seasonal vaccines too often. As Tom noted, it was exactly this kind of technology that might have obviated the problem they had with this mismatch. I think that is why these kinds of technologies are so important.

But I believe I am quite comfortable in making recommendations for the H1N1 vaccines that are out there now, because we have a long track record of that process and the safety profile that goes along with them. So I think that as we see this in the future, it is going to be as important that we have the same kinds of confidence in the safety that we might be recommending for a vaccine that we might be recommending for many more people.

So in my mind the votes and the bars were interesting. I think this shouldn't be at least from my perspective an indication that this is not a technology that we are all very interested in and want to promote. I want to help as much as possible, but at the same time we want to make sure that if we are going to be making recommendations for a vaccine like this in many people, we feel as confident about it as we do about the current vaccines.

DR. DEBOLD: I think the lost to follow-up issue is bigger than -- it is a very big issue for me. Some of the kinds of conditions that I worry about are things that might crop up and become obvious 28 days after vaccination and then some. The autoimmune issues, they are not going to necessarily be apparent within a few days of vaccination. So this needs to have very active follow-up for a good period of time.

I know you guys mentioned that there was some

compensation for research subjects. Maybe if their compensation didn't happen up front, perhaps there is a way to motivate continued participation over the long haul.

DR. FLEMING: I won't repeat what I have already said, but just to add a couple of additional thoughts. First of all, I want to state as Dr. Gellin stated that my sense as his is that this is a technology and this is an intervention that deserves further pursuit. So while I have concerns, these aren't concerns that the data is saying that this is unfavorable to benefit to risk. It is more the concern that we don't adequately understand, and I hope it is pursued.

One of the ways we often think about pursuing safety issues that aren't adequately understood is through pharmacovigilance, through postmarketing, often through single-arm trials. It is important to understand where those are useful and where they are not useful. Where they are useful is when what you really care about are increases in event rates that are of large relative risk. Intussusception with the rotovirus was detected appropriately with postmarketing pharmacovigilance. It was at least a tenfold relative increase. PML can be detected without a control arm in Crohn's disease and MS patients because it is a thousand fold relative increase. Pharmacovigilance works for that.

We have had discussions today about whether the hypersensitivity type reactions and the pericarditis, are

those causally influenced by the vaccine or, while they are rare events, still could have been part of the natural history. Those are the kinds of things you can't answer if a relative risk increase of two or three would be really important. You can't discern that from an uncontrolled experience. It is the reason now that there are so many large scale trials that are being done pre- and postmarketing for safety.

I have mentioned the COX-2 inhibitors. The COX-2 inhibitors induced, at least Vioxx and Bextra, about a 1.5 fold increase in the relative risk of cardiovascular death, stroke and M.I. That is on a baseline rate in OA and RA patients of ten per thousand person years. 1.5 is five per thousand. That is very important in benefit to risk. There is no way to sort that out from no increase, because when such events occur, you don't know whether or not it is due to the intervention or due to natural history.

So my worry is, there are some events here that we have seen that are rare but are extremely important, and they do occur though in natural history, and you are not going to be able to sort out whether they are vaccine induced or just natural history with an uncontrolled pharmacovigilance postmarketing study.

DR. LEVANDOWSKI: I don't really have anything to add to what has been very eloquently stated already by

everybody here. But I would like to support the product in the sense that it is a new technology that does hold a lot of promise, and should help to move influenza vaccines towards some future goal of not only robustness, but more availability, particularly for those people who may have some allergies to the existing vaccines. That I think would be a very important thing.

DR. SANCHEZ: When I received the information about this vaccine, I was very excited because of the need for having a non-egg based one. I think that has all been discussed. I know even in my own NICU, where egg allergies is the reason why some do not receive it.

Overall though, as I read through the information, I was actually somewhat disappointed. I think I expected it to be better than the Fluzone, and I think what we are seeing is a similar product.

I think that overall, I don't see that as a reason not to approve the vaccine or to say that I am in agreement with its licensure. However, I do agree with everyone else that the safety needs to be looked at in postmarketing.

DR. WHARTON: We have more information about safety in the 18 to 49-year-old population and older age groups. The issue of hypersensitivity I think can be addressed postlicensure, but it definitely needs to be addressed.

Another issue with this technology that I would

like to put out because I'm not sure it has been explicitly stated is, there could be circumstances where it is very important to be able to make influenza vaccine in substrates. This will be our vaccine that could do that, should it be licensed, and that indeed could be very important for public health.

DR. STAPLETON: Dr. McInnes, any additional comments? Dr. Rennels, would you like to comment from the industry perspective? No. Dr. Baylor, does that help? Yes. Are there any additional comments? If not, then we will adjourn. Thank you for your thoughtful input.

(Whereupon, the meeting was adjourned at 3:00 p.m.)