FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

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MEETING

OPEN SESSION

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THURSDAY, JANUARY 25, 2007

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The meeting came to order at 8:00 a.m. in the Grand Ballroom of the Doubletree Hotel, 8120 Wisconsin Ave, Bethesda, MD. Ruth A Karron, MD, Chair, Presiding.

PRESENT:

RUTH A. KARRON, MD, CHAIR
CHRISTINE WALSH, RN, EXECUTIVE SECRETARY
MONICA M. FARLEY, MD, MEMBER
PHILIP S. LARUSSA, MD, MEMBER
CINDY LYN PROVINCE, RN, MSN, MAMEMBER
STEVEN SELF, PHD, MEMBER
BONNIE WORD, PHD, MEMBER
JOHN MODLIN, MD, MEMBER
WALTER ROYAL, III, MD, MEMBER
LINDA JACKSON, MD, MPH, MEMBER
JACK STAPLETON, MD, MEMBER
SETH HETHERINGTON, MD, INDUSTRY REPRESENTATIVE
JAY BUTLER, MD, FAAP, FACP, TEMPORARY VOTING MEMBER
BRUCE GELLIN, MD, MPH, TEMPORARY VOTING MEMBER
ERIK HEWLETT, MD, TEMPORARY VOTING MEMBER
PAMELA MCINNES, DDS, MSC, TEMPORARY VOTING MEMBER
MELINDA WHARTON, MD, MPH, TEMPORARY VOTING MEMBER

A G E N D A

P R O C E E D I N G S

(8:09:07 a.m.)

CHAIR KARRON: Good morning, everyone. I'd like to ask everyone to please take their seats, and I would like to call the meeting to order, and welcome you to the first VRBPAC meeting of 2007. I'd like to now call Dr. Baylor to the podium to present plaques to our retiring members.

(Presentation of Appreciation Plaques.)

CHAIR KARRON: Thank you, Dr. Baylor. I'd now like to turn the meeting over to Christine Walsh, the Executive Secretary, for some announcements.

MS. WALSH: Good morning. I'm Christine Walsh, the Executive Secretary for today's meeting of the Vaccines and Related Biological Products Advisory Committee. I would like to welcome all of you to this meeting of the Advisory Committee. Today's sessions will consist of presentations that are both open and closed to the public.

I would like to request that everyone please check your cell phones and pagers to make sure they are off or in the silent mode. I would now like to read into public record the conflict of interest statement for today's meeting.

"The Food and Drug Administration (FDA) is convening today's meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the industry representative, all members and consultants of the committee are special government employees, or regular federal employees from other agencies, and are subject to the Federal Conflict of Interest laws and regulations.

The following information on the status of this Advisory Committee's compliance with Federal Ethics and Conflict of Interest laws, including, but not limited to, 18 USC 208, and 21 USC 355(n)4 is being provided to participants in today's meeting, and to the public.

FDA has determined that members of this Advisory Committee and consultants of the Committee are in compliance with Federal Ethics and Conflict of Interest laws, including, but not limited to, 18 USC 208, and 21 USC 355(n)4. Under 18 USC 208, applicable to all government agencies, and 21 USC 355(n)(4), applicable to certain FDA committees, Congress has authorized FDA to grant waivers to special government employees who have financial

conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest, Section 208, and where participation is necessary to afford essential expertise, Section 355.

Members and consultants of the Committee who are special government employees at today's meeting, including special government employees appointed as Temporary Voting Members, have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their employer, spouse, or minor child related to Topic I - Discussion and recommendation on the safety and immunogenicity of DTaP-IPV/Hib vaccine for the protection of infants and young children against diphtheria, tetanus, pertussis, and Hib, Pentacel, sponsored by Sanofi Pasteur Limited.

Topic II is the presentation on the research programs in the Office of Vaccines Research and Review. These interests may include investments, consulting, expert witness testimony, contacts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves the discussion

and recommendation on the safety and immunogenicity of a DTaP-IPV/Hib vaccine, Pentacel. In accordance with 18 USC Section 208(b)(3), waivers were granted to Dr. Lisa Jackson, Dr. Ruth Karron, and Dr. John Modlin. Dr. Seth Hetherington is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Inhibitex, Incorporated. 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 and consultants that if the discussions involve any other products or firms not already on the agenda, for which an FDA participant 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 relationships that you may have with the sponsor, its product, and if known, its direct competitors."

That ends the reading of the conflict of interest statement. Dr. Karron, I turn the meeting over to you.

CHAIR KARRON: Again, I would like to welcome you all to this meeting of VRBPAC for January 25th, and I would like to ask each of the committee members to introduce themselves, and tell us where they're from. Dr. Modlin, we'll begin with you.

DR. MODLIN: Good morning. This is Dr. John Modlin from Dartmouth Medical School.

DR. HEWLETT: Gary Hewlett from the University of Virginia.

DR. McINNES: Pamela McInnes, National Institutes of Health.

DR. ROYAL: Walter Royal, University of Maryland School of Medicine.

DR. STAPLETON: Jack Stapleton, University of Iowa College of Medicine.

MS. PROVINCE: Cindy Province, St. Louis Center for Bioethics and Culture.

DR. JACKSON: Lisa Jackson, Group Health Center for Health Studies.

DR. WORD: Bonnie Word Baylor, College of Medicine, Texas Children's Hospital.

DR. HETHERINGTON: Seth Hetherington from Icogen Research, Triangle Park, North Carolina.

DR. SELF: Steve Self, Hutchinson Cancer Research Center in Seattle.

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

DR. LARUSSA: Phil Larussa, Columbia University College of Physicians and Surgeons, New York.

DR. BUTLER: Jay Butler, Alaska Division of Public Health.

DR. FARLEY: Monica Farley, Emory University in Atlanta.

CHAIR KARRON: We'll let Dr. Gellin get to the podium and introduce himself.

DR. GELLIN: Another just in time delivery. Bruce Gellin, National Vaccine Program Office, Department of Health and Human Services. Apologies.

CHAIR KARRON: Thank you, Bruce. And I'm Ruth Karron from Johns Hopkins University. So we'll begin the morning session today, which is to evaluate the safety and efficacy of Pentacel, and I'm first going to ask Dr. Theresa Finn to come forward and provide the introduction from the FDA.

DR. FINN: All right. The vaccine we'll be presenting and discussing today is Pentacel, manufactured by Sanofi Pasteur Canada. Pentacel is a combination vaccine which contains diphtheria and

tetanus toxoids, acellular pertussis antigens, inactivated polio virus, and the capsid polysaccharide from Haemophilus influenza Type B conjugated to tetanus toxid. Okay?

It's for intramuscular doses at 2, 4, 6, and 15 to 18 months of age. The DTaP-IPV component of Pentacel is supplied as a liquid formulation, which is used to reconstitute the lyophilized polysaccharide conjugate vaccine to form Pentacel, which I have abbreviated here on this slide as DTaP-IPV/Hib.

The presentations today will describe the safety and efficacy data provided to support licensure of Pentacel. Evaluation of the efficacy of the diphtheria, tetanus, polio, and Hib components of Pentacel is based upon immunogenicity using established protective antibody levels or GMCs relative to separately administered vaccine components. There is no generally accepted correlated protection for pertussis; therefore, efficacy of the pertussis component is based upon a serologic bridge to DTaP vaccine called Daptacel. The first bridge is historical to Daptacel administered in the Sweden-1 Pertussis Efficacy Trial, and the second bridge is to Daptacel

administered to U.S. children in a randomized study.

Following the presentations and discussion, the committee will be asked the following questions and discussion items. The first one is, are the available data adequate to support the safety of four doses of Pentacel administered at two, four, six, and fifteen to eighteen months of age, and this is a voting item. If the available data are not adequate, what additional data are needed? The second item is, please discuss whether the available data are adequate to support the efficacy of the diphtheria, tetanus, and polio components of Pentacel, (b) the Hib, or otherwise also known as PRP-T component of Pentacel, and (c), the pertussis component of Pentacel. And then there is a voting question; are the available data adequate to support the efficacy of Pentacel? And if the available data are not adequate, what additional data are needed? And the last item is a discussion item; if Pentacel is licensed, please identify any issues which should be addressed in post licensure studies.

So that concludes my very brief introduction of the morning session. And unless there are any questions for clarification, I'd like to turn the podium over to Sanofi Pasteur

representative.

DR. KUYKENS: Members of the Advisory Committee, ladies and gentlemen, good morning. I'm Luc Kuykens, Vice President of Regulatory Affairs for Sanofi Pasteur, and we are pleased today to have the opportunity to present Pentacel, our infant and toddler tetanus, diphtheria, acellular pertussis, polio, and Haemophilus influenza conjugate combination vaccine. Following my introduction, I will present the safety profile of Pentacel. Dr. Decker will review the immunogenicity data of our application. Dr. Scott Halperin will give you an overview of nine years of post marketing experience with Pentacel in Canada, and Dr. Greenberg will address the current epidemiology of pertussis and Hib disease in the U.S.

Given time constraints, our presentation will focus on the key data today, and the complete overview of the clinical data was available in your briefing documents.

Why did Sanofi Pasteur develop this combination vaccine? As the first candidate, DTaP-IPV/Hib combination vaccine in the U.S., Pentacel offers unique benefits for the entire immunization community. Patient benefits by providing the

greatest shot reduction compared to any other single combination vaccine, and a well-established safety profile after nine years of experience in Canada with over 12 million doses distributed. Healthcare provider benefits, by optimizing the implementation of immunization guidelines, and simplifying administration. And public health benefits, by potentially improving vaccination coverage rates, and timeliness, as well as vaccine supply. Dr. David Greenberg will elaborate on these important points later in his presentation.

Pentacel is based on a liquid combination vaccine of tetanus, diphtheria, pertussis and IPV antigens, also called Quadracel, which itself is a licensed vaccine in Canada. Quadracel is used to reconstitute active prior to injection. The composition of Pentacel for diphtheria and tetanus reflects a current U.S. standard of care on licensed pediatric DTaP vaccine, Daptacel. The antigen concentrations for IPV and Haemophilus influenza match licensed polio vaccs and active vaccines, and the pertussis antigens are the same as in Daptacel and Adacel.

Sanofi Pasteur's five component pertussis vaccine is unique in that it contains fimbriae types

II and III, as well as PT, FHA, and Pertactin. The importance of the fimbriae components was confirmed in the Aracel complex study nested in the Sweden-I pertussis efficacy trial. In addition, these results show that multiplicity of responses to the pertussis antigens and their interactions contribute to the overall efficacy of the vaccine. And only PT antibody titers were high efficacy was 46 percent, if either Pertactin or fimbriae were high, efficacy was between 72 to 75 percent, and when both were high, efficacy was 85 percent.

The goal of our clinical development program was to demonstrate the safety and immunogenicity of the combination vaccine Pentacel, compared to the standard of care, and also to the Sweden-1 Infant Efficacy Trial for pertussis, which has shown 85 percent efficacy against WHO defined pertussis. In addition, we compared the consistency of three Pentacel lots. And, finally, we studied the concomitant administration of Pentacel with Hepatitis B, pneumococcal conjugate, MMR and Varicella vaccines.

The indication requested today is for active immunization against diphtheria, tetanus, pertussis, polio and Hib. We have a four-dose

series, beginning in infants at age two months, and we have a four-dose given between 15 and 18 months of age.

Today we will present data from five different clinical studies considered pivotal for U.S. licensure. The first two studies, P3T-06 and 494-01, were controlled studies. Study P3T-06 compared Pentacel to the standard of care. You will note the abbreviation SC on subsequent slides for this group. 494-01 was the Pentacel lot consistency study that also compared Pentacel to its formulation equivalent components. This control group is later abbreviated FE. The next two studies, M5A07 and 494-03, investigated the lack of interaction after the concomitant administration of Pentacel with Prevnar, MMR, and Varivax vaccines. And, finally, Study 5A99-08 compared the administration of a fourth dose of Pentacel at 15 to 16, versus 17 to 18 months of age.

The composition of Pentacel compared to the vaccines used in the control studies was as follows. Study P3T-06 compared Pentacel to Daptacel, IPOL and ActHIB, licensed standard of care vaccines in the U.S. Study 494-01 compared Pentacel to its formulation equivalent components, HCPDT, Poliovax, and ActHIB. HCPDT is an unlicensed product

manufactured especially for this study to match the Pentacel composition, and it's not used in any other setting.

Of the pivotal studies, three included both infants and toddlers, P3T-06, 494-01, and 494-03. M5A07 is a recent Prevnar interaction study for which only immunogenicity data in infants were included in this application. The infant data obtained from these four studies provide us with Pentacel safety data in close to 4,200 infants, and immunogenicity data in almost 2,700 infants. Immunogenicity data were generated in subsets of the studies. Four of those data were collected in more than 5,000 toddlers for safety, and 2,800 for immunogenicity across four studies, the three previously mentioned that included both infants and toddlers, and Study 5A9908, a specific toddler study. In total, more than 19,000 doses of Pentacel were administered to infants, and 6,900 to toddlers in the U.S. licensure trials.

The results of the clinical trials demonstrate that Pentacel was safe and well-tolerated, and achieved safety and immunogenicity profile similar to that of the current standard of care. Pentacel can be given concomitantly with

Hepatitis B pneumococcal conjugate MMR and Varivax vaccines, and Pentacel has controlled Hib and pertussis disease in the target population through nine years of exclusive use in Canada.

At this point, I would like to review the clinical safety data of our application. The key objectives of the safety assessment were to compare the safety profile of Pentacel to that of the control vaccines. Secondly, to characterize the overall safety profile of Pentacel given separately or simultaneously with other recommended vaccines. The safety population analyzed consisted of all participants that received at least one dose of vaccine. For the remainder of the clinical safety presentation, I will always present infant data first, followed by toddler data for each of the different safety parameters.

Starting with immediate reactions, these were collected for 30-minutes, post vaccination. For all data slides, we will be presenting Pentacel data from the two control studies, P3T-06 and 494-01 to the left, data from the two control groups in the middle, and Pentacel data from the non-controlled studies to the right. Less than .1 percent of Pentacel recipients and .2 percent of control vaccine

recipients experienced at least one immediate reaction during the infant series. There were no anaphylactic reactions reported, and no immediate reaction was classified as a serious adverse event. All results without sequella.

After a fourth dose for the controlled studies, the rates of immediate reactions in Pentacel recipients versus control were similar. We noticed a higher rate of reactions in one non-controlled study, 494-03; however, upon further investigation, the majority of these were actually local injection site reactions of short duration, and mild in severity, reported as immediate reactions by some of the investigators. There were no anaphylactic reactions reported, no immediate reaction was classified as a serious adverse event, and all resolved without sequella.

Solicited local reactions were collected on a daily basis on a diary card, from days zero to seven after vaccination. The pre-established list of reactions contained redness, injection site swelling and tenderness for all four doses, and for the fourth dose specifically, change in limb circumference. Information on the severity of each of these reactions was collected on a daily basis, and this

allowed us not only to determine the overall duration of an event, but also the duration of the most intense portion of the reported event.

On this graph, we analyzed the percentage of participants reporting solicited local reactions over time after vaccination. Rates for Pentacel during the infant series were only elevated during the first three days after vaccination. We made a similar observation after the fourth dose.

A second question we examined was whether there was an increase in local reactogenicity by dose, from dose one to three. Importantly, we did not see an increase in local reactogenicity after each subsequent dose in the infant series for local redness, swelling, or tenderness.

I will now review the data for local injection site swelling. Rates observed for local injection site swelling were similar or lower after Pentacel vaccination compared to control vaccines. This was true both in the infant series, also after the fourth dose. Most reactions were mild or moderate in nature. We reached the same conclusion for local redness and injection site tenderness. I will not present those data, they were included in your briefing document. After the toddler dose, we

specifically examined changed in limb circumference. Rates were similar across studies, and between Pentacel and control vaccines.

The pre-established list of solicited systemic reactions contained fever, infant being less active, crying, fussiness, vomiting, diarrhea, anorexia, and rash. Information on presence and severity of these reactions was collected on a daily basis for seven days on a diary card, and the safety comparison objective for systemic reactions in pivotal trials P3T-06 and 494-01 was to demonstrate that Pentacel is non-inferior to control vaccines with regard to the portion of participants reporting any fever. Increased rates of fever compared to baseline were observed in the first two days after vaccination during the infant series regardless if after Pentacel or control vaccines.

Historically, there has been a concern about increased fever rates associated with combination vaccines versus their components during the infant series. Fever rates observed after the administration of Pentacel in the infant series were generally similar or lower compared to the separately administered control vaccines. Fever rates did slightly increase by dose, the majority of reported

fevers were mild or moderate in nature.

Non-inferiority for fever rates in Pentacel recipients and the two control studies were shown after each of the doses in the infant series. When looking at fever rates after the four dose, large majority of cases were reported within two days of vaccination, similar to what we saw in the infant series. Rates of fever were comparable across Pentacel and control groups. Most episodes of fever were mild or moderate in nature.

The upper limit of the 90 percent confidence interval of the difference in rates of any fever between Pentacel and control was lower than 10 for both control studies. The higher rate seen in P3T-06 after Pentacel was solely caused by mild fevers. We did not observe any differences between Pentacel and control groups for all the other solicited systemic reactions. Those data were provided for your information in the briefing document.

Moving to non-serious unsolicited adverse events, these were collected from day zero to seven after vaccination on diary cards, and during telephone contacts, or site visits through day 60 after vaccination for those events requiring a

medical contact. Overall rates were similar between Pentacel and control groups. Most non-serious unsolicited adverse events were common childhood conditions, the majority of which were assessed as non-related to vaccination by the investigators.

Among the unsolicited, adverse events were some specific events of special interest that we analyzed separately in this population. These were hypotonic-hyporesponsive episodes, hypotonias, and seizures. Overall rates were very low, and similar between Pentacel and the control groups, within seven days after vaccination during the infant series. In the infant series, there were no reports of HHE or febrile seizures. Rates of hypotonia, non-febrile, and possible seizures were low and comparable between Pentacel and the control groups. After the fourth dose seen on this table, no HHE, hypotonias, non-febrile or possible seizures were reported. Rates for febrile seizures were similar between Pentacel and control vaccines.

We collected serious adverse events during the whole study period, and analyzed them for up to 60 days after each dose. Rates for SAEs were similar between Pentacel and control vaccines, and all but one SAE was considered unrelated to

vaccination by the investigator. This one SAE was observed in the control group of Study P3T-06, and was a febrile seizure with apnea that occurred 12 hours post-dose one, and considered probably related by the investigators. The participant was not hospitalized for this episode, and recovered fully without sequella.

There were three deaths reported across the U.S. licensure trials in infants. All three were considered unrelated to vaccination, one was a case of a car accident 22 days after vaccination of Pentacel, one was a SIDS, 52 days after vaccination of Pentacel, and one was a case of ependynoma, diagnosed 54 days post vaccination of the control vaccines in Study P3T-06.

All SAEs reported after fourth dose were considered not related to vaccination by the investigators. In the control studies, the rates of SAEs were similar between groups in the first two months after vaccination. However, between two and six months after vaccination, the nine studies in P3T-06 were mainly upper respiratory infections and pre-existing congenital malformations.

Two deaths were reported around the fourth dose of the pivotal studies, first one

occurred during or between the infant series and the toddler dose, and was a case of neuroblastoma, first diagnosed in a nine-month old male leading to his death at age 15 months. The second was a case of suffocation nine days after the fourth dose of Pentacel. Both were considered unrelated to vaccination.

Now in addition to the valuable clinical safety data collected, we have access to extensive post-marketing safety data through the exclusive use of Pentacel in Canada for over nine years. Pentacel was introduced in Canada in May 1997, and has been used exclusively since 1998. Approximately 12.5 million doses have been administered using a vaccination schedule similar to the U.S. one. Post-marketing safety data for passive surveillance of inherent limitations, including under-reporting, and lack of denominative data. However, these systems are very valuable in detecting safety signals for clinically significant events.

From May 1997 through April 2006, Sanofi Pasteur received 288 safety reports. Most reports received, 221, were non-serious, 67 were reported as serious adverse events. The most commonly reported adverse event was an injection site reaction. Other

frequently reported adverse events were in line with what has been observed in our controlled clinical trials, and did not indicate any unexpected safety signal in a post-marketing setting.

We also analyzed the same categories of events of special interest in this population, same as we studied in our clinical trials. The number of reported events of HHE, seizures, and deaths over a period of nine years were low, and well below the number of expected cases based on the literature for such events.

In conclusion, in clinical trials, Pentacel was safe and well-tolerated among infants and toddlers, and its safety profile was similar to the standard-of-care vaccines. As demonstrated by the data presented in your briefing document, Pentacel can be given either simultaneously, or separately from Hepatitis B, Pneumo conjugate, MMR, or Varicella vaccines. The safety profile of Pentacel in Canada, where more than 12.5 million doses have been distributed since 1997, confirms the clinical safety data from the trials.

At this point, I would like to invite Michael Decker to the podium, and Michael will review the immunogenicity data of our application.

DR. DECKER: Thanks, Luc. I'm Dr. Michael Decker, and I'll present to you the immunogenicity data that we have in support of the Pentacel licensure application. There are a number of different types of immunogenicity data I will present to you, including geometric mean titers, which are the log normalized average antibody levels, and are primary endpoint for all of the antigens. Four-fold rises, which are the proportion of participants whose post-immunization titer is at least four times their pre-immunization titer, and this is a primary endpoint for the pertussis antigens. Seroprotection rates for those antigens which were seroprotective levels are defined, including diphtheria, tetanus, Hib, and polio. This is the proportion of participants whose post-immunization antibody level equaled or exceeded the defined threshold.

For the pertussis antigens, an analogous measure is the vaccine response rate. Specific protective levels are not defined for the individual pertussis antigens, but this gives an analogous measure, and these data, in the interest of time, are more fully presented in the briefing document, rather than in my slide presentation. We have

available for all the antigens reverse cumulative distribution curves which provides you a graphical evaluation of the antibody distribution in the entire population.

And, finally, I'll present to you data from the serological bridge to efficacy, which is the basis for determination of the efficacy of an acellular pertussis vaccine by bridging the serological data from a U.S. study population to the serological data from the population that was included in the original efficacy trial.

I'll present the data in the following order. First, the pertussis antigens, second Hib, third diphtheria and tetanus, fourth polio, and finally co-administration of Pentacel with other licensed vaccines. Let's start with Study P3T06, which was a multi-center randomized and controlled study involving nearly 2,000 infants vaccinated at two, four, six, and 15 to 16 months of age. Approximately a quarter of these infants received Pentacel, and the other three-quarters each received one of three lots of Daptacel, along with IPOL and ActHIB. Daptacel, IPOL, and ActHIB represent the current U.S. license standard of care regime. This was also a Daptacel lot consistency trial, and that's

why there were three groups for Daptacel.

I'm going to show you a number of slides that look this. For pertussis, we have four pairs of bars, in blue the Pentacel recipients, on this slide in yellow the children received Daptacel, IPOL, and ActHIB. To the right, we've got the FIM responses, FIM-II and FIM-III assayed together, so it's shown as a single FIM response, and the Y axis for that response is different than the Y axis for the other three antigens, because FIM antibody levels numerically are much higher, so to show them on a single slide, they have different scales. Whenever I show you a slide like this, below the slide there's a table of the actual numerical results, so this particular slide shows you the geometric mean titers post `03; in other words, following immunization at 2.6 months of age with Pentacel, or with the U.S. licensed standard of care vaccines. You see here that the antibody responses are similar between Pentacel and the U.S. licensed standard of care for Pertactin or FIM, higher for Pentacel than for the current U.S. licensed standard of care for PT and FHA. This slide shows the four-fold rise rates. The results are similar to what you just saw, although closer together in each comparison for each antigen

than the GMTs.

Now you've already seen a few slides like this. This one is a little bit more complicated. Let me explain to you what this is. It's a graphical display of the results of the statistical non-inferiority test, so along the left are the names of all the comparisons being made. I've got two horizontal X axes here, the one in white is the axis of ratios. It's appropriate to a comparison of GMTs. The one in yellow is the axis of proportions, an arithmetic axis that's appropriate to the comparison of rates or proportions. The vertical white line to the right is aligned with 1.5 on the GMT ratio, or 10 on the rate difference ratio, and that's the limit of non-inferiority. If this was a lot consistency slide, there would be a similar, second line to the left marking the other side of the lot consistency comparison. And then displayed in the body of the slide are the point estimates for each ratio or rate difference, along with their 90 or 95 percent confidence limits as may be appropriate, based on whatever was pre-agreed. So in this particular slide, we see arrayed the results of the post dose three pertussis evaluations for Pentacel versus the U.S. standard-of-care vaccines. And as you see, all

12 comparisons met the predefined criteria for statistical non-inferiority.

Here are the geometric mean titers post-dose four in Study P3T06, PT and FIM responses are very similar, Pentacel's response is higher for FHA, Daptacel response is higher for Pertactin. Four-fold rise rates are very similar across the four antigens. Eleven of the twelve non-inferiority tests were met, one was not for Pertactin GMT. The point estimate for that ratio was 2.0; whereas, the limit for non-inferiority was 1.5.

Now this slide is a little bit different from what I've shown you before. The Canadian five-component pertussis vaccines are five-component vaccines because each component has been shown to contribute to the protective efficacy, so one of the questions is relevant is, to what extent does a vaccinee respond to one, two, three, four, or all five antigens? And this looks at that question, and compares the results for the group receiving Pentacel, versus the group receiving Daptacel, IPOL and ActHIB. And, as you see, the results are very similar for all the possible combinations here, perhaps a little bit better for Pentacel, for response to all the included antigens.

I mentioned before the serological bridge to efficacy. Between 1992 and 1995, the Swedes conducted an NIH-sponsored efficacy trial that evaluated several vaccines head-to-head, including Daptacel. The vaccines were administered at two, four, and six months of age. Follow-up was conducted over a two-year period and demonstrated 85 percent efficacy of Daptacel against WHO-defined or classic pertussis, whooping cough, as well as 78 percent efficacy against pertussis of any severity defined as a laboratory confirmed-infection associated with at least one day of cough.

The Swedes bled the children at one of their participating sites, and those serological specimens became the basis for the serological report in the Swedish efficacy trial. And those serum samples were provided to us to be used for bridging studies for U.S. licensure of acellular pertussis vaccines. So pertussis antibody levels in the Swede-1 efficacy trial were compared to those following four doses of Pentacel in our studies P3T06, which I just showed you, and 49401, which I'll show you in a minute. The sera were tested contemporaneously in the same laboratory, under the same conditions, and using the same validated assay. And here are the

results of the comparison between the Pentacel recipients in Study P3T06, shown again in blue, and in the bright green, the Swedish children who participated in the efficacy trial. As you see, Pertactin results were reasonably similar, a little bit higher in the Swedish kids; whereas, PT, FHA, and fimbriae results were substantially higher in the U.S. kids for Pentacel.

Here are the results of the statistical non-inferiority testing for the serological bridge to efficacy. Eleven of the twelve comparisons met the predefined criteria, one was borderline for the Pertactin four-fold rise. 49401, as Dr. Kuykens mentioned, was a Pentacel lot consistency trial, primarily. It also involved a comparison to the separate constituent components of Pentacel. The randomized trial involved over 3,500 infants who were vaccinated at two, four, six, and 15 months of age. About 60 percent of the children received Pentacel, about 40 percent received HCPDT, which is the unlicensed and unmarketed DTaP constituent component of Pentacel, Poliovax, which is licensed in both U.S. and Canada, but not used in either country as a stand-alone vaccine, only used as a constituent component of the combinations, and ActHIB given

separately.

As in Study P3T06, all of the subjects received Hepatitis B vaccine at birth, two, and six months of age, and most subjects received concomitant Prevnar. Here are the results of the lot consistency evaluation. All 32 comparisons meet the statistical criteria for consistency. Here are the results for the geometric mean titer ratios, geometric mean titers post-dose three for the comparison of the Pentacel recipients to the children receiving the separate constituent components of Pentacel. The results are very similar for all four antigens. Four-fold rise rates also similar, and all 12 predefined statistical non-inferiority criteria were met.

Following the fourth dose of Pentacel, geometric mean titers were as shown, very similar between the Pentacel recipients and those receiving a separate unlicensed or licensed components for PT and FHA, a little bit higher for the separate components for Pertactin, higher for Pentacel for FIM. Four-fold rise rates were very similar across all four antigens. Eleven of the twelve comparisons met the predefined criteria for non-inferiority, one, Pertactin GMT, was borderline.

Here are the results of the comparison of the Pentacel recipients in Study 49401 to the Swedish children in the Sweden-I efficacy trial. As you saw earlier for P3T06, the results are fairly similar for Pertactin, a little bit higher in the Swedish kids, higher for the Pentacel recipients in the U.S. kids for FIM, PT, FHA. Four-fold rise rates show a similar pattern, although the differences are smaller. And here are the results of the statistical non-inferiority testing. Eleven of the twelve comparisons met non-inferiority, one, Pertactin four-fold rise rate, did not. That one was also borderline on the P3T06.

Now since the GMTs met non-inferiority, and the four-fold rise did not, which is a comparison of post- to pre-antibody levels, this suggests that there might have been a difference in pres, so we looked at that. And this slide shows the distribution of pre-antibody titers that are higher than four times the lower limit of detection. What you see is that in the U.S. study population, 11 percent of the kids had pre-immunization antibody titers that were higher than four times the lower limit of detection, but it was only one kid in Sweden had such an elevated pre titer. If those elevated

pre titers are excluded from the calculation, it turns out that non-inferiority would have been met, so from this we conclude that the failure of non-inferiority in both of these comparisons reflects not a lowered response to the vaccine, but rather a higher pre-immunization titer in a subgroup of the population.

This is reverse cumulative distribution curve. It gives you a graphical overview of the distribution of antibody in the titer study population. Arrayed on the left vertical axis is the percent of the participants who achieved any given antibody level, and on the horizontal axis, the antibody level achieved. So, for example, 100 percent of the kids had at least one unit of antibody, zero percent of the kids had 10,000 units of antibody, and the curves connect all the lines in between.

Now this particular slide shows you the post- dose four pertussis toxin antibody levels for the Pentacel recipients versus the Sweden-1 kids. The heavy white line is the reference. That's the PT antibody levels in Sweden-1. The thin, colored lines each represent one of the Pentacel licensure trials. So for this particular slide, what you see is that

all the Pentacel results are very similar, the curves have the same shape, they're fairly closely clustered, and all align to the right of, meaning, therefore, they're superior to or they dominate the curve for Sweden-1. That's PT. Here's FHA. All the Pentacel curves lie to the right of the Sweden-1 curve. For Pertactin, the Pentacel curves bracket the Sweden-1 curve, overlie it in part. For FIM, the Pentacel curves, some overlie, most are to the right of the Sweden-1 curve.

Now the children who participated in studies P3T06 and 49401 have continued to grow. Right now, they're in the four to six-year old age range, and they're due for another dose of vaccine, so to take advantage of that, all the participants in P3T06 and 49401 were invited to participate in follow-up studies called P3T10 and P3T11, respectively, that gave them a fifth dose of vaccine, specifically Daptacel. Now these studies are both currently underway, but quite recently, the serological data from the pre-fifth dose bleed became available. And what is pre-fifth dose for these two new studies, of course, for P3T06 and 49401, is long-term follow-up to the booster dose, so we thought that would be of interest to you.

On this slide, we've got four triplets of bars. The first bar in each triplet is the kids who got Pentacel in Study 49401. The middle bar in each triplet is the kids who got Pentacel in Study P3T06, and the right-hand bar is the kids who received Daptacel. So, as you see, at four to six years of age, there was excellent persistence of antibody, really very similar across all three groups.

Let's turn now to the HIB antibody results. P3T06, you recall, was the comparison of Pentacel versus the U.S.-licensed standard of care, Daptacel, IPOL, and ActHIB. On this slide, we see the HIB antibody responses, the proportions achieving the predefined seroprotective levels of .15 micrograms per ML post dose three, 1.0 microgram per ML post dose three, and 1.0 microgram per ML post dose four. As you see, the results were essentially identical between Pentacel and the current U.S.-licensed standard of care.

Here are the geometric mean titers post dose three, post dose four. They're identical post dose three. They're similar and quite high post dose four, being 18 for the Pentacel group, and 20 for the Daptacel, IPOL, and ActHIB group. All predefined statistical non-inferiority criteria were met.

49401, you recall, was primarily a lot consistency trial for Pentacel, and with respect to the HIB component, here are the results of that lot consistency trial. Eight of the nine comparisons fell within the consistency boundaries, one was borderline. Here are the data that underlie that borderline result. It was the comparison of these two. But you'll notice here are the GMTs, over here are the proportions achieving defined protective levels. You'll notice that they're very similar for those two groups, and quite high. And, therefore, we think that borderline result on consistency is of no clinical importance.

49401 also involved a comparison of Pentacel to its separately administered licensed or unlicensed constituent components. Here are the results of that comparison for the proportion achieving seroprotective titers, post dose three and post dose four, organized as before. The results are very similar across the three comparisons.

We see a different picture with the geometric mean titers, post dose three and post dose four. Geometric mean titers are nearly twice as high in the kids receiving the separate constituent components, as in the kids who received Pentacel. Of

interest, though, is that the Pentacel recipients in 49401 had geometric mean titers very similar to those of the Pentacel or the Daptacel recipients in Study P3T06. But because the separate licensed or unlicensed component group had such high titers, the GMT comparisons all failed non-inferiority. The proportion achieving seroprotective levels of .15 post dose three, or 1.0 post dose four, did achieve non-inferiority.

Now when we received these results, it was very hard for us to interpret them because of the fact that not only is HCPDT not a licensed vaccine used anywhere in the world, but there, to our knowledge, has never been any other study in which children were given concomitantly HCPDT, Poliovax, and IHIB, neither by us, nor by any independent investigator, so we had no context in which to interpret this and try to understand why this unexpected high antibody response for HIB in the separate components group arose.

Historically, we know that HIB antibody responses have shown high variability from study to study. This has been a phenomenon since we first began following HIB vaccines, and part of that variability was addressed by the efforts by the CBER

Laboratories and others to standardize the assays. But even after that work was accomplished, there's been extensive variability in HIB results. In order to try to understand what's going on here, we broadened our view to look at our complete database of HIB results. Shown on this scatter plot are the results for HIB antibody for every study that we've conducted of Pentacel in North America. Shown to the left are the results for Pentacel, shown to the right are the results for separately administered components or vaccines. Now, you'll notice the 49401 results are clearly a high outlier in this group. There's a similar high outlier in the Pentacel group, not in the same study, though. The range of results for Pentacel looks just like the range of results for ActHIB. We see that post dose three for the GMTs. We see it post dose four for the GMTs.

Now I mentioned variability of HIB results, and let me give you a striking example of that. You recall that in Study P3T06, the seroprotection rates and GMTs were almost perfectly identical between the Pentacel group and the separately administered Daptacel, IPOL, and ActHIB group, overall. Shown on this scatter plot are the sites, the individual study sites that had at least

10 participants, at least participants to ensure that the GMT was reasonably stable. Notice the scatter ranges from just over one to almost six. The range, again, looks identical for the Pentacel group, and the ActHIB group, as you'd expect, since the overall GMTs were the same. Now at this point, any reasonable person would assume that this is a site, and those are its two values. This is a site, and those are its two values. This is a site, and those are its two values, and so on. That's what you'd think; that's not the case. This is a site, and that's a Pentacel value, and here is its ActHIB value. This is a site, that's its Pentacel value, and here's its ActHIB value. Had we done the study just here, you'd have one strong impression, had we done it here, you'd have another strong impression, the opposite one. And I have no explanation for this variability in HIB results, but it's something that we always see. These kids were randomized at each of these sites. There should be no difference. There was randomization within each site. There should be no difference in the demographic characteristics, but we do see this kind of variability.

Now, fortunately, this was a very large study. It was conducted at many sites, so the

overall average is pretty stable. A lot of the earlier studies and literature were conducted at a single site, and they were larger than one of these. Another way to look at the data we have is as shown on this slide. Again, what we have here is every study we've ever done with Pentacel in Canada or the United States. The bars show, in this case, the HIB GMTs post dose three. The bars are arrayed in chronological order. Again, in the blue we have the Pentacel results, in the yellow we have the results for separately administered components or vaccines. What you see is not only are the range of results essentially identical for Pentacel and separate vaccines, but the temporal sequence is very similar, the patterns are identical. We see for the GMTs post dose three, GMTs pre-dose four, GMTs post dose four, and we see it for the GMTs pre-dose five.

Now seroprotection rates do not vary as much as GMTs, but they still vary. And you see that the pattern of variation is identical for Pentacel and for separate components, as is the range of results post dose three, pre-dose four, and, note, very high seroprotective levels pre-dose four. Post dose four, essentially 100 percent, and pre-dose five, so by four to six years of age, well over 90

percent of all the children still have seroprotective levels.

Now we thought of one other way to give you insight into how Pentacel's HIB performance compares to that of the current U.S. licensed standard of care. P3T07 and M5A07 are both studies that were designed to evaluate whether Prevnar interfered with the DTaP vaccines. P3T07 was a post licensure commitment trial for Daptacel. M5A07 was a pre-licensure study for Pentacel. The studies were conducted at more or less the same time, overlapping time periods, at overlapping sites, sometimes even the same sites across the United States, so from each of these studies, we have a group that received the DTaP vaccine, Pentacel or Daptacel with Prevnar, and another group that received it without Prevnar. So what I've done here is I've rearranged those results so that on this slide, you see the Pentacel kids who did not get Prevnar, versus the Daptacel kids who did not get Prevnar, and what you see here is that the proportion achieving seroprotective levels of .15 or 1.0 micrograms per mL are very similar, perhaps even a little bit higher in the Pentacel group, and the GMTs are similar, perhaps a little bit higher in the Pentacel group. Now if we look at the kids who got

Prevnar at the same time, we see very similar results, so this is one more body of data to suggest that Pentacel reduces HIB responses that are essentially identical to the regimen currently used in the United States.

Finally, the reverse cumulative distribution curves, shown in the heavy white, is the reference. The children who received the U.S. licensed standard of care vaccines, Daptacel, IPOL, and ActHIB in Study P3T06. The thin colored lines, again, represent the Pentacel recipients in the various U.S. licensure trials. You'll notice that all of the Pentacel curves are closely clustered, reasonably parallel, and they overlie or are to the right of the standard of care reference group.

Turning now to diphtheria and tetanus immunogenicity, on this slide we look at, again, Study P3T06, the comparison to the current U.S. standard of care. The left-hand half of the slide is diphtheria, the right-hand half of the slide is tetanus. Within each half, the first pair of bars is the proportion achieving .01 IU per mL. Second pair of bars is the proportion achieving one. All these numbers are very close to 100 percent both for Pentacel and for the Daptacel, IPOL, ActHIB group.

Post dose four, similar results. Study 49401, post dose three, similar results, post dose four, similar results. All pre-specified non-inferiority criteria were met.

Polio, all the results are on this single slide. The first three pairs of bars are the results for P3T06 post dose three. The middle three pairs of bars are 49401 post dose three, and the final three pairs of bars are 49401 post dose four. The proportion seroprotective is essentially 100 percent all the way across. And, accordingly, all pre-specified non-inferiority criteria were met.

Finally, co-administration of Pentacel with other licensed vaccines. Most of these data are in your briefing document. In the interest of time, I will only present to you selected results, and what I selected, because I thought it would be the most interesting, are the interaction with Prevnar questions, so we start with Study P3T06. In P3T06, everybody received Prevnar at two, four, and six, concomitantly with either their Pentacel on the one hand, or their Daptacel, IPOL, and ActHIB on the other. This slide shows you the Prevnar antibody responses. For the seven Prevnar antigens, two results are shown: the proportion achieving .15, the

proportion achieving .50, and as you see, Prevnar performs identically, whether you give it with Pentacel, or you give it with Daptacel, IPOL, and ActHIB.

49403 looked at the same question, but at the toddler dose. Now in 49403, Pentacel was given at 15 to 16 months of age, and the Prevnar was given either at that time or it had been given earlier at 12 months of age. So here, the blue bars represent the kids who got Pentacel with their Prevnar, and the gold bars represent kids who got no Pentacel with their Prevnar, instead, they got MMR Varivax with their Prevnar. As you see, whether you give your Prevnar with Pentacel, or you give your Prevnar with MMR Varivax, the Prevnar performs identically.

M5A07, which we talked about earlier, looks at the other side of the question, does Prevnar interfere with Pentacel? This is post dose three pertussis GMTs in blue, the kids who got Prevnar with their Pentacel, in white the kids who got no Prevnar with their Pentacel. Pentacel performs identically whether or not you give Prevnar at the same time.

Now the FDA briefing document noted that, at the time that was written, the fourth dose data were not yet available, and FDA was concerned that

their might be evidence of interaction with fourth dose. But quite recently, the fourth dose data became available. They were submitted, in fact, to CBER this week, and here they are. At the fourth dose, whether you get Prevnar with your Pentacel, or you get no Prevnar with your Pentacel, the Pentacel performs the same. HIB, same story. The HIB component of Pentacel performs the same, whether you give Prevnar with it, or you don't give Prevnar with it, post dose three, and post dose four.

So based on all the data I've shown you, I offer the following conclusions. First, Pentacel's efficacy against pertussis is confirmed based on the favorable serological comparison to the Sweden-1 efficacy trial. Pentacel producted pertussis GMTs and sero response rates comparable to those seen with separately administered vaccines, with a good similarity of responses demonstrated across all the U.S. licensure trials, as shown by the reverse cumulative distribution curves. There was good antibody persistence for all antigens up to four to six years of age, and Pentacel produced diphtheria, tetanus and poliovirus seroprotection rates comparable to those seen with separately administered vaccines.

With respect to HIB, Pentacel produced HIB GMTs and seroprotection rates that were comparable to separately administered U.S. licensed standard of care vaccines. They were similar across a full range of Pentacel studies, and very high following the fourth dose, and levels that persisted well into the pre-school booster age.

Pentacel can be co-administered with other routinely recommended infant and toddler vaccines, and so with respect to immune responses, Pentacel is a suitable replacement for separately administered Daptacel, IPOL, and ActHIB.

I would now like to ask Dr. Scott Halperin to come to the podium and present to you the data from the Canada epidemiological surveillance.

DR. HALPERIN: Thank you, Michael. You've seen now the clinical trial data to see how the vaccine has performed under research conditions. What I'm now going to show is how Pentacel has performed in the real world for the past nine years in Canada under routine use.

Pentacel was licensed in Canada in May 1997, and it was introduced province-by-province between July 1997 and April 1998. The vaccine that Pentacel replaced was another combination vaccine

against the same five diseases, but it contained the whole cell pertussis vaccine, instead of an acellular pertussis vaccine component.

Pentacel has a universal indication, and has been the only vaccine used in Canada to prevent pertussis and Hib among young children. The schedule in Canada is very similar to that in the U.S. Pentacel is given at two, four, six, and 18 months of age. Quadracel, which is Pentacel without the Hib component, is given as a booster dose at four to six years of age.

Over the next several slides, I will show you the Pertussis and Hib epidemiologic data from Canada with the universal use of Pentacel. In Canada, we have a national passive surveillance program for pertussis conducted by the Public Health Agency of Canada. Just as in the U.S., the incidents of pertussis dropped dramatically after the introduction of wholesale Pertussis vaccine in the 1940s. Also similar to the U.S., in Canada we experienced a resurgence of pertussis in the 1990s, which I will show you in more detail on the next slide.

The highest rates of pertussis occur among Canadian infants less than one year of age.

The majority of these cases are in the age group of infants less than six months of age, which are those too young to have completed the infant series. The next two curves represent children one to four years of age, and five to nine years of age.

As in all countries, an epidemiologic cycle of pertussis occurs every three to five years, shown here in 1990, 1994, and 1998. Since the last peak in 1998, the rates among children one to four, and five to nine years of age, have decreased by 80 to 90 percent. The last peak occurred just as Pentacel was being introduced, and no peak has occurred since then. We would have expected another peak to occur in these age groups sometime between 2001 and 2003, based on the three to five year cycle that we'd seen previously, but none has materialized to-date.

The decline of pertussis in the preschool and young school age children, the prevention of widespread outbreaks has been -- is the first time this cohort has been without these outbreaks, and it's been associated with the use of Pentacel vaccine.

In addition to the national passive surveillance, we have a longstanding hospital-based

active surveillance program in Canada known as the Immunization Monitoring Program Active, or IMPACT. IMPACT comprises 12 pediatric medical centers accounting for 90 percent of Canada's tertiary care pediatric beds. Patients are referred to IMPACT centers from all Canadian provinces and territories, and at each IMPACT site, a nurse monitor conducts prospective active surveillance.

Along with David Scheiffley, the co-principal investigator of the IMPACT network, and we recently reviewed our experience with hospitalized pertussis before and after the implementation of Pentacel. On this slide, the left half represents the wholesale vaccine era, 1993 to 1997. The right side represents the acellular Pentacel vaccine era, 1998 to 2005. And this dotted line represents the transition period during which Pentacel was introduced province-by-province.

The peak in 1998 right here represents the same naturally occurring epidemiologic peak that I showed for the national data. The slides show how the number of cases declined during the Pentacel era, with virtual elimination of the expected cyclical peak. In fact, amongst a subset of children one to four years of age, the incidents of pertussis

declined 85 percent during the Pentacel era, compared to the previous era.

In addition to the national IMPACT data, information is also available from a number of individual provinces and territories. One example which I show here in the slide comes from the Northwest Territories. The distribution of pertussis cases from 1993 to 1996 when wholesale pertussis vaccine was used serves as the baseline.

Following the introduction of Pentacel in 1997, substantially fewer cases occurred amongst infants less than one year of age, and one to four years of age. Notice that there was minimal effect on the children five to nine years of age, because these older children had not yet been given Pentacel.

During 2001 to 2004, the number of cases declined even further among all age groups. Relative to 1993 to 1996, the baseline year, the number of cases occurring in 2001 to 2004 declined by 90 percent in one to four, and five to nine-year olds. In fact, now you can see that the big decline of cases in the five to nine-year old age group, because by this last time period these children had received four doses of Pentacel, demonstrating the full

clinical benefit of the series.

Now I'd like to move on to show you the Hib epidemiologic data from Canada. The Public Health Agency of Canada also conducts national passive surveillance for invasive Hib disease. Hib conjugate vaccines were introduced for toddlers in 1998, and for infants in 1992. As a result, the incidents of invasive Hib disease in children less than five years of age decreased dramatically during the early 1990s. Since Pentacel was introduced in 1997, the incidences remained at extremely low rates; that is, an average of less than one case per 100,000 population per year.

Active surveillance for Hib is also one of the targets of the IMPACT hospital network reported over the past 20 years. The number of Hib cases decreased from 485 cases in 1985, to an average of fewer than 10 cases per year since the introduction of Pentacel in 1997.

Further, since 1997, most invasive Hib disease has occurred in children who are unimmunized, partially immunized, or have severe underlying medical conditions, such as immunodeficiencies. These active surveillance data from IMPACT confirm the national surveillance data demonstrating the

ongoing control of invasive Hib disease in Canada.

In fact, during a five-year period from 2001 to 2005, only 34 cases were reported to the IMPACT network. Of these, 11 were amongst First Nation and Inuit children. Canadian Aboriginal populations, like Native American children in the U.S., are at very high risk of developing invasive Hib disease, far greater than the non-Aboriginal populations. Two of the First Nation and Inuit children were unvaccinated, seven were partially vaccinated, and two had received three doses. One of these two had a history of recurrent pneumonias. Thus, there were only two breakthrough cases of invasive Hib disease amongst this very high-risk population over a five-year period.

In addition to the national and IMPACT surveillance systems, there's yet a third surveillance system in Canada. The Public Health Agency of Canada and the Arctic Investigations Program of the CDC maintained a joint surveillance covering the polar regions of two countries, referred to as the International Circumpolar Surveillance System.

The First Nation and Inuit population in the polar regions of Canada is about 75,000

individuals. The Native American population of Alaska is about 120,000. During five years of surveillance, Pentacel was used in Canada, and PRP-OMP was used in Alaska. In Canada, only four cases of Hib disease were reported to the ICS system among children five years of age and under. Three were Aboriginal. In Alaska, seven cases were reported, and six were Native. Therefore, Pentacel protects very high-risk children against Hib disease, as well as PRP-OMP.

By coincidence, our National Advisory Committee on Immunization a couple of weeks ago reviewed the Canadian experience with combination vaccines, and specifically reviewed the experience of Pentacel over the past nine years. This is what they said. "Combination vaccines against diphtheria, pertussis, polio, tetanus and Hib infections have been the standard for routine primary immunization of infants in Canada. Like its monovalent constituent vaccines, Pentacel has been highly successful in controlling these infectious diseases in Canada, but has the additional benefit of fewer injections." This statement by our National Advisory Committee perhaps has some relevance for the discussions today.

In conclusion, in Canada we have

extensive clinical experience with the exclusive use of Pentacel over a nine-year period with more than 12 million doses distributed. National IMPACT and regional surveillance data confirm very low rates of pertussis and Hib disease amongst young infants, or infants and young children. Pentacel provides sustained protection against pertussis through nine years of age. Pentacel provides excellent protection against invasive Hib disease. Hib cases are rare in Canada, even amongst our First Nation and Inuit populations, and over the past five years, only two to three breakthrough cases among these high-risk children have been identified by two surveillance systems.

At this point, I'd like to ask David Greenberg to come up, and he'll bring us back from Canada to look at the U.S. situation.

DR. GREENBERG: Thank you, and good morning. Dr. Halperin has shown you how Pentacel has successfully controlled Pertussis and invasive Hib disease in Canada. I'm going to show you how the Canadian experience relates to what we would expect with the use of Pentacel in the U.S. The epidemiology of pertussis and invasive Hib disease in the U.S. will be presented, and compared to the

Canadian experience. The potential benefits of Pentacel to patients, healthcare providers, and public health will be reviewed, including the prospect for fewer injections, and improved compliance. And I'll show you how Pentacel would fit into the U.S. immunization schedule, and potentially improve coverage rates and timeliness of vaccinations.

Shown on this slide is the epidemiology of pertussis in the U.S. since the 1920s, as reported by the CDC. In the inset, is comparable epidemiologic data for this disease in Canada during the same time period. You can see how the general pattern is similar in the two countries.

Just as in Canada, the highest incidents of pertussis in the U.S. occur among infants less than six months of age. But as these data from 2005 demonstrate, pertussis occurs among all age groups. Now one would think the children six months of age and older would have received the full infant series of pertussis vaccine, but among the cases in the six to eleven month age group, over half, 55 percent have not yet received three doses of DTaP vaccine.

Now let's take a look at Hib disease. Dr. Halperin showed you the excellent control of Hib

disease in Canada, and a similar pattern can be seen in the U.S. Just as in Canada, national passive surveillance data demonstrate steadily improving control of Hib disease among infants and young children in the U.S. over the past dozen years. Improved control of Hib disease can also be seen with active surveillance data. As shown here from the CDC's active bacterial core, or ABC's surveillance system. In the inset, one can see similar decrease in cases of Hib disease with the active surveillance system in Canada, IMPACT. And just as in Canada, the majority of Hib cases in the U.S. occur among children who are unvaccinated, or only partially vaccinated. And, of course, ActHIB is the same Hib vaccine that's contained in Pentacel.

For the past decade, the market share of ActHIB has doubled; therefore, ActHIB has become the dominant standard of care Hib vaccine during the time of excellent control of Hib disease in the U.S.

In summary, the epidemiology of pertussis is similar in the U.S. and Canada. In Canada, Pentacel has led to sustained protection against Pertussis through nine years of age. The epidemiology of invasive Hib disease is similar in the U.S. and Canada. ActHIB is the dominant standard

of care Hib vaccine used in the U.S., and ActHIB and Pentacel is the exclusive Hib vaccine used in Canada. In light of these data, Pentacel is expected to perform as well in the U.S., as it has in Canada.

Now let's turn our attention to the immunization schedule. Shown on this slide is the 2007 U.S. recommended childhood immunization schedule through 18 months of age. The schedule has become progressively more complicated over time. For this reason, the ACIP, AAP, and AAFP recommend the use of combination vaccines. In their recommendations, they state to minimize the number of injections children receive, use of licensed combination vaccines is preferred over separate injection of their equivalent component vaccines. And, certainly, the immunization schedule is far more complicated now than it was in 1999 when these recommendations were issued.

Now let's look at the Public Health ramifications of our complex schedule, and the potential benefit of combination vaccines. The CDC used the data from the 2003 National Immunization Survey of over 14,000 children to assess immunization rates. Remarkably, the CDC found that only 17 percent of 24 to 35 month old children were immunized on time for six routinely recommended childhood

vaccines. These children are under-vaccinated for a mean of 172 days. Three-quarters of the children were delayed for at least one vaccine, and 37 percent were severely under-vaccinated, that is for greater than six months for at least one vaccine. For individual vaccines, the CDC reported that the timeliness was best for IPV, in which 9 percent were severely under-vaccinated, but the timeliness was much worse for the DTaP and Hib vaccines, 16 and 21 percent were severely under-vaccinated.

If Pentacel is used at the first and every opportunity to vaccinate, then coverage rates and timeliness would be optimized, and would be identical for all three of these vaccines. Indeed, existing data demonstrate the combination vaccines improve coverage rates and timeliness. In this study, the Georgia Medicaid data for children born in 2003 were analyzed to assess coverage rates of children at two years of age. Children who were in the combination cohort received at least one dose of DTaP-IPV Hepatitis B vaccine. Children in a separate vaccine cohort received separate vaccines and were matched to the combination group by age, gender, and race. The coverage rates for DTaP, Hepatitis B, and IPV were all significantly greater for children who

received the combination vaccine, than those that received separate vaccines. In addition, the timeliness of vaccination was significantly better for those that received the combination product.

Now other countries have struggled with complicated immunization schedules, and the experience in Germany is directly applicable to the U.S., but unlike the U.S., they introduced progressively higher valent combination vaccines over the past decade. Using National Immunization Survey Data, they assessed coverage rates among children 15 months of age during 1996 to 2003. Starting with the Hib component, you can clearly see how coverage rates steadily and significantly climbed with the introduction of each new higher valent Hib-containing combination vaccine. A similar pattern can be seen for IPV and Hepatitis B, and the coverage rate significantly climbed once each component was incorporated into the combination.

Now let's return to the immunization schedule. The question is what combination vaccine would benefit our patients. Lots of combinations are possible, but not all would make much sense. For example, Pneumococcal influenza combination vaccine wouldn't have much utility because of the differing

immunization schedules, but it makes a lot of sense to combine DTaP, Hib, and IPV because these three vaccines tend to be given at the same time during the immunization schedule. By using Pentacel, Hepatitis B can be given on an optimal schedule, including the birth dose, and properly spaced second and third doses to maximize the immunologic response to this vaccine.

In addition, Pentacel would reduce number of injections. Up to 23 separate injections are given to comply with the U.S. immunization schedule. Combination vaccines can reduce the number of injections, as I'll show with several examples. TriHIBit, or DTaP-Hib vaccine saves one shot; Comvax, Hib-Hepatitis B vaccine saves three shots; Pediarix, DTaP-IPV/Hepatitis B saves five shots, and Pentacel saves the greatest number of shots, seven. So, in conclusion, Pentacel is the first candidate DTaP-IPV/Hib combination vaccine in the U.S. Potential benefits to patients include maximum shot reduction, and a safety profile that encourages compliance; and, therefore, protection against serious infectious diseases, including Pertussis and invasive Hib disease.

Benefits to the healthcare provider,

including optimal implementation of immunization recommendations, and simplified administration, because Pentacel combines three vaccines that are routinely given together. And benefits to public health, including expected improvement of coverage rates and timeliness, facilitation of an optimal Hepatitis B schedule, and improved combination vaccine supply for the infant series.

Now I'll ask Dr. Kuykens to return and conclude our presentation.

DR. KUYKENS: Thank you, David. Pentacel safety data have shown that it was safe and well-tolerated among infants and toddlers with a safety profile similar to the current U.S. standard of care vaccines. Pentacel can be given either simultaneously or separate from Hepatitis B, pneumo conjugate, MMR, or varicella vaccines.

Immunogenicity data presented by Michael for pertussis seen after Pentacel administration compares variably to the Sweden-1 efficacy trial. Hib GMTs and seroprotection rates were comparable to the U.S. current standard of care vaccines, and Pentacel has shown similar immune responses when given alone, or concomitantly with Hepatitis B, Prevnar, MMR, and Varivax vaccines.

After nine years of exclusive use of Pentacel in Canada, it is shown to be safe and effective in controlling pertussis and Hib disease. And Pentacel is expected to perform as well in the U.S. as in Canada, given the similar epidemiology of pertussis and Hib between the two countries. Its adoption will reduce the number of injections for infants and toddlers, and its fit with the U.S. immunization schedule will facilitate inclusion of new vaccines.

The introduction of Pentacel has the potential to improve timeliness and coverage of vaccination.

This concludes the presentation of Sanofi Pasteur, and we'll be happy to answer clarifying questions from the committee.

CHAIR KARRON: Thank you, Dr. Kuykens. Are there questions from the Committee at this time?

DR. McINNES: I have two questions. The first deals with the haemophilus DMTs, and I notice your breakdown is by 0.1 micrograms per milliliter and 1.0 micrograms per milliliter. Do you have data around the 0.5 micrograms per milliliter range?

DR. DECKER: No, we don't. Indeed, I've never heard that asked. I don't believe we've ever done an analysis where we took 0.5 as a cut point.

In fact, I've never heard that asked before, so it catches me by surprise.

DR. McINNES: I'm sorry, but, I mean, the rationale would be that I think we're familiar, those who've lived through the haemophilus wars of the genesis of the 0.1 and the 1.0. However, I think there is a fair amount of discomfort on relying solely on the 0.1 in thinking about the fact that in the pathogenesis of invasive haemophilus disease, you would probably like to have a significant amount of antibody around. It may not need to be as high as 1.0, as long as you also have induction of a booster response. And so I think certainly in smaller immunogenicity studies, 0.5 has been looked at, so I was just wondering if you did have anything like that.

My second question is, I am wrestling with trying to understand the bridging of post four dose data in Pentacel to post three dose data from Sweden.

DR. DECKER: I'll be happy to answer that, but I just have a question for CBER and the Chair, because right now, my understanding of our instructions, we're only supposed to answer questions where if you didn't understand the slides.

DR. McINNES: All right. So could we look at slide C63?

DR. DECKER: All right. Because I can answer this, but it will more than consume the time allotted for clarifying questions.

DR. McINNES: Sure.

DR. DECKER: And perhaps we ought to leave it for the full question and answer period afterwards.

DR. McINNES: Sure. I wanted to confirm that this is post four dose data Pentacel, versus post three dose data for Sweden.

DR. DECKER: Yes, it is.

DR. McINNES: Essentially, 16 or 17 or so months old children, versus seven month olds. Is that correct?

DR. DECKER: Yes, it is.

DR. McINNES: Thank you.

DR. DECKER: And if you'll ask that question later, I'll show you what you are implying you'd like to see.

CHAIR KARRON: Dr. Larussa.

DR. LARUSSA: Two minor questions. Michael, when you talked about the amount of tetanus toxoid similar in Pentacel as with the component

vaccines, does that also include the contribution from PRPT?

DR. DECKER: Well, what I talked about with the antibody responses; so, of course, the antibody responses are global.

DR. LARUSSA: No, no, I meant the quantity of tetanus toxoid.

DR. DECKER: I didn't talk about that, Luc did in the first slide.

DR. LARUSSA: Okay.

DR. DECKER: And what's listed in that slide is the -- for the tetanus component is the nominal tetanus component. It does not include whatever might be contributed by the PRPT. But, of course, if that PRPT is having an effect, either additive or interference, then you would see it in the antibody slides that I did show, and you don't see that.

DR. LARUSSA: And one other clarification; just to be clear, when you calculate the geometric mean titers, the negatives are included in the calculation of the titer, the non-responders.

DR. DECKER: The non-responders, yes, they are. And in my experience, it's almost always a predefined algorithm for handling those, whether you

take them as being one-half the lower limit of detection, or you take the lower limit. And, honestly, I don't know what was pre-agreed with CBER on that. If you want to know, we'll find out, because whatever it was, it was pre-arranged.

CHAIR KARRON: Dr. Butler.

DR. BUTLER: Thank you, Dr. Karron. A question for Dr. Halperin. Trying to draw an analogy and look at a comparison between the Alaska Native population and the Inuit, aboriginal, and Mattee population of the territories, it appears - and I realize the numbers are very, very small, so rates may be unstable, but it appears that the rates in Canada in the aboriginal population are on the order of about twice what they are in the Native population in Alaska. Most of the invasive Hib cases in Alaska Natives are true vaccine failures occurring in children who are completely immunized. It appears that the majority, or at least seven of eleven in Canada are occurring in children who received one or two doses. Actually, the slide just before that one. I guess I'm trying to see if I've got this right, that you're probably seeing more cases that are occurring in children who've received only one or perhaps two doses of Hib vaccination.

DR. HALPERIN: Yes. In this slide, what you see, the rates for the Canadian Native population are three of 75,000, and here it's six of 120,000, so the rates are approximately similar. What you saw before on the slide from the IMPACT data, the IMPACT data is not just the circumpolar, so those are aboriginal, First Nation, Inuit population throughout Canada that are referred to the IMPACT centers. And there, that's where you had the 11 vaccine, or Hib cases, of which most of those were unimmunized or under-immunized children.

DR. BUTLER: I guess what's not on that slide is we haven't had a case of invasive Hib disease in a native child living in an urban area of Alaska for a long time, and I think rural Alaska is much more like the territories than Anchorage is. There's no cities of that size, or that degree of development in the territories, so that's where I'm working in that our rates in rural Alaska are considerably higher. So the denominator I'm working from, that's a little different.

CHAIR KARRON: I'd actually like to ask you a question, Dr. Halperin, while you're here. Could you comment on when Prevnar was introduced in Canada, and then when it had widespread use relative

to your surveillance data?

DR. HALPERIN: Yes. Prevnar was introduced in Canada. Again, in Canada, everything is done province-by-province, territory-by-territory, so widespread use of Prevnar was in 2005, so it's been a year and a half now. But our first province did it much earlier, which was Alberta, and the data that we've seen in Alberta - now we're already seeing the effects of Prevnar with decrease in invasive pneumococcal disease, and no change in rates of pertussis and haemophilus influenza invasive disease. The rest of the provinces, the rest of the national data, it's too soon from the implementation to see. It's only Alberta that has implementation long enough to make those type of observations.

CHAIR KARRON: Dr. Hewlett.

DR. HEWLETT: I'd like to ask Dr. Halperin a clarification also about the data. I think the two slides that you show of incidents data in Canada on page C131, and C133 - the C131 has specific age groups involved, and C133, I just want to make sure that's total number of cases?

DR. HALPERIN: Yes. The 133 is from IMPACT centers, so that's our active surveillance system. That's the total number of cases seen in

those IMPACT hospitals. The rates which are 131, are from their national data.

DR. HEWLETT: Okay. And I'm just trying to get a sense -- I know that you've had an adolescent booster for a while. I don't remember how many years, and I'm trying to factor that into the decreased total number of cases in the IMPACT.

DR. HALPERIN: Yes. Within the IMPACT data, the Adacel, the implementation of the adolescent vaccine is now about three years into that, three or four years into that, and that has had a remarkable effect on the older age groups, as well, so we were seeing these shifts before Adacel, so what we were seeing is control of the disease in the children, cohorts that received Pentacel, but then a residual of cases in the older age groups, those eight, ten, and above. We have had some early data that shows that now we've seen that sort of peak in the pre-adolescents, adolescents is also starting to go down in provinces that have initiated the adolescent dose first.

DR. HEWLETT: So C133 is reflective of impact of both of those, presumably.

DR. HALPERIN: That's right. The data that we have from IMPACT here are before the

implementation, so it's only in that last year where we've had adolescent doses.

DR. HEWLETT: Okay. Yes, that's what I was getting. Thank you.

DR. MODLIN: A question for Mike. All of the data in composite seem to suggest that there is some small effect on Pertactin levels, of interference. Do you have any sense of what the basis for that may be? I'm not sure this is a major issue, but I'm sure you've thought about it a little bit when you compare Pentacel with the same vaccine given separately.

DR. DECKER: Again, John, as with Pam, would you come back with that question in the main question and answer period, because I actually have a very good answer for that, but then I'm meeting CBER presentation guidance.

DR. MODLIN: Fair enough. One other question, and maybe this is more appropriate for later on, too. Do we have data from the infant series on infants that received fewer than three doses in terms of immunogenicity, will we see any of that?

DR. DECKER: I wouldn't think so. Of course, we don't allow that to happen in the studies,

and I doubt that the National Surveillance Data breaks it out that way. We'll think about that, but the answer probably is no, such data are not available. Actually, John, I correct myself. I do have data on that. It's part of -- it will be shown as part of my answer to Dr. McInnes' question, and it will also answer your question.

CHAIR KARRON: Dr. Farley.

DR. FARLEY: Another question about the Canadian data. I think it was 134 where you were showing an impressive decline here. Can you tell us - this is just numbers of cases. Did the coverage rates change when you introduced Pentacel, because I think that's -- I mean, you need to put it in the context of whether we had better coverage at that point.

DR. HALPERIN: As opposed to the situation that U.S. has, which Dr. Greenberg was expressing about going from multiple injections to a single injection - in Canada we didn't have that situation, so we went from a five disease covering wholesale containing vaccine called Penta, to an acellular pertussis containing vaccine called Pentacel, so we had no change in injections when we went from the wholesale to the acellular era, and the

switch to Pentacel. And we did not see any change in coverage rates based on Canadian data looking at coverage rates. There wasn't a change in coverage rates over that period.

CHAIR KARRON: I have two just very brief questions. One is for Dr. Decker, and it relates to the bridging study that you described. And in that, you talked about individuals, children who had high levels of Pertactin antibody prior to immunization, and that the failure and the percent responders was accounted for when you pulled those out. If you look at the geometric mean titers once you've pulled those individuals out, those children with high pre-existing antibody titers, and you compare those to the Sweden trial, how did those compare?

DR. DECKER: The -- if you pull out -- well, let me back up a little bit. The children who -- let me back up even further, I'm sorry. Something that we've got to remember, the four-fold rise doesn't tell, or what CBER calls seroconversion rate, which we're calling four-fold rise, tells you nothing about whether the vaccine is protecting anyone. If you start way low and you go up to four times that, and you're still way low, you're not protected. If you start way high, and you go up twice that, and

you're still above the protected level, you're protected. It tells you nothing about protection. What it does tell you is whether overall the vaccine appears to be benefitting most of the recipients. You don't want a vaccine that only a third of the people you give it to have any benefit, the other two-thirds only suffer safety effects, and they get no benefit, so that's what four-fold rise is good for.

Now with that in mind, going back to the data we have, slide on please, the kids shown in the blue dots on the left, the U.S. kids - we're a much more heterogeneous population than Sweden. It's not really surprising that we've got more heterogeneous pretiters, kids coming out of environments that differ a lot from the fairly homogeneous Sweden population, and the very homogeneous medical care system in Sweden. All right, so we've got these heterogeneous pretiters. Those kids with the blue dots have post titers that were fine. They were two-fold, three-fold higher, but just weren't four-fold higher. If you pull them out of the GMTs, you don't have a material effect on the GMTs because the post immunization GMTs were similar between these kids and the kids who do not have high pretiters, so the

vaccine is performing fine, and it's carrying everybody up to the protective level, but some kids start high enough that it's not four times higher.

CHAIR KARRON: And just a very quick safety question, I think, for Dr. Kuykens; which is, I noticed in the briefing book that children, some children have axillary temps taken, and some had rectal temps. And I think I understand that the distribution between groups among those who got axillary and rectal temps was approximately equal. Is that true?

DR. KUYKENS: In the infant series it's approximately equal, then for the four dose it's more axillary, which was also recommended in the protocol. For toddlers, it was allowed to take temperatures axillary. I think what's important, we analyzed the data was axillary and rectal, and the conclusion did not change, so if you saw the overall fever rates that Pentacel was similar, lower than the control groups, that held both for axillary and for rectal, and we have dose analysis, and we can show those later if you'd like to see them.

CHAIR KARRON: Dr. Modlin.

DR. MODLIN: Just one other quick -- it would be of interest to see the actual GMTs for DT

and polio, not necessarily right now. Maybe just the reverse distribution curves would be sufficient, but I think it would be of interest to see them.

DR. DECKER: Again, if you'll make a note in case I don't remember it. Ask me that when we get into the main Q&A.

CHAIR KARRON: Dr. Wharton.

DR. WHARTON: Another question about the Canadian data. Slide 135 appears from just looking at the graph that following a NADR in 1999 or 2000, there actually has been a very modest, perhaps a very modest increase in invasive haemophilus influenza disease. Am I misreading this?

DR. HALPERIN: No, there does seem to be a very gradual increase there. One of the problems with the national data is that it's invasive haemophilus influenza disease, and not all provinces are typing before they submit that information for the national statistics. From the IMPACT data, we've also looked at that, and we have seen an increase in HIA cases. And in the IMPACT data, we don't see this increase. What we see is just a little bit up and down that we're seeing in the U.S., as well, so we think that's an effect of a non-typable contribution.

CHAIR KARRON: We're running a little bit behind schedule, but we will take a 15-minute break, and ask people to be back here by about 10:15. Thank you.

(Whereupon, the proceedings went off the record at 9:58:12 a.m., and went back on the record at 10:24:56 a.m.)

CHAIR KARRON: We're going to go ahead and resume the session with the FDA presentation, and Dr. Farizo will start.

DR. FARIZO: It's based upon data from four pivotal studies, which will be the focus of my presentation. In addition, I'll provide an overview of the post marketing safety experience with Pentacel, primarily in Canada. For the sake of time, I'll not present data from historical non-IND studies on approximately 1,600 subjects who received three or four consecutive doses of Pentacel. FDA's briefing document for the Committee includes a summary of serious adverse events from these studies, and the type of serious adverse events reported were generally similar to those reported in the pivotal studies.

In the next few slides, I'll review the design of the pivotal studies, the overall safety

database, safety monitoring procedures, and subjects disposition and demographics.

Of the four studies, two were randomized controlled studies, one of which is shown in this slide. In Study 49401 conducted in the U.S., the safety of four doses of Pentacel was compared to separately administered formulation equivalent vaccines, HCPDT, Poliovax, and ActHIB. Poliovax and ActHIB are licensed in the U.S., although only ActHIB is distributed. The controlled DTaP vaccine, HCPDT, as you've heard, is not licensed in the U.S. It differs from U.S. licensed Daptacel only in that it contains higher amounts of PT and FHA.

Now I'm going to digress from the slide for just a moment to note that safety data on HCPDT were considered supportive for licensure of Daptacel in the United States. And under the Daptacel BLA, CBER reviewed data on serious adverse events from the Sweden-II Efficacy Trial in which more than 20,000 infants received HCPDT predominantly on a three, five, twelve month schedule. Approximately 2,500 received HCPDT at two, four, and six months of age. And, in addition, the Daptacel BLA included comparative safety data on more common adverse events following HCPDT or Daptacel from smaller studies. A

summary of the safety data on HCPDT from the Sweden-II trial was included in the FDA briefing document.

Now returning to Study 49401, the study vaccines were administered at two, four, six, and 15 months of age. Prevnar was introduced shortly after the study was initiated, and was given concomitantly with the first three doses of Pentacel or control vaccines in roughly 80 percent of subjects. The first dose of hepatitis B vaccine was administered shortly after birth, the second and third doses were with U.S. licensed Recombivax HB administered concomitantly with Pentacel or control vaccines. Approximately 2,500 subjects received Pentacel, and approximately 1,000 control vaccines.

In Study P3T06, also conducted in the U.S., the safety of four doses of Pentacel was compared to separately administered Daptacel, ActHIB, and IPOL, all of which are licensed in the U.S. Study vaccines were administered at two, four, six, and 15 to 16 months of age, except for IPOL, which was not given at 15 to 16 months. All subjects received Prevnar concomitantly with Pentacel or control vaccines at two, four, and six months, and Recombivax HB was administered concomitantly at two and six months. The control group is larger than the

Pentacel group, because, as Dr. Decker pointed out, evaluation of lot consistency was a primary objective of this study, so approximately 1,400 subjects received Daptacel, and 485 received Pentacel. Control subjects were randomized to different dose four groups to evaluate concomitant immunization with Daptacel, and only those who received Daptacel and ActHIB alone, 418 at 15 to 16 months of age served as the control group for the fourth dose of Pentacel.

Now in U.S. Study 49403, subjects received four doses of Pentacel, all received concomitant Prevnar at two, four, and six months of age, and either two or three doses of Recombivax HB concomitantly with Pentacel. Subjects were randomized to receive the fourth dose of Pentacel alone, concomitantly with MMR and Varivax, or concomitantly with Prevnar. Approximately 1,200 subjects received Pentacel. There was no separately administered vaccines control group. And in Study 5A9908 conducted in Canada, approximately 1,800 toddlers who had previously received three doses of Pentacel, received a fourth dose. So across the four pivotal studies for safety, a total of 5,980 subjects received at least one dose of Pentacel, roughly 4,000 were from studies of four consecutive doses, and

approximately 1,800 were from a study of the fourth dose only. Overall in these studies, just over 17,000 doses of Pentacel were administered.

Safety monitoring was similar across the four studies. Subjects were observed at the study sites for 30 minutes post vaccination. Solicited local reactions and systemic events were recorded daily on diary cards for days zero to seven post vaccination. Serious adverse events were monitored through 60 days following the last dose of study vaccines in three studies, and through 180 days following the last dose in Study P3T06.

Periodic phone calls to inquire about adverse events were conducted at approximately day two to four depending on the study, and days eight, thirty, and sixty following each dose. And, also, approximately six months after the last dose in Study P3T06.

This slide shows the number of subjects who participated in the pivotal studies, and the proportions of those completing the specified safety follow-up. In the first three studies shown, approximately 85 to 93 percent of subjects completed the sixty day follow-up post dose three, and 68 to 86 percent completed the sixty or one-eighty day follow-

up post dose four. In Study 5A9908, in which subjects received only the fourth dose of Pentacel as part of the study, more than 99 percent completed the 60-day follow-up. Although not shown on the slide in both Pentacel and control subjects, the majority of early discontinuations were due to voluntary withdrawal or non-compliance.

In the U.S. studies, approximately two-thirds of subjects were Caucasian, approximately 10 percent black, 15 percent Hispanic, roughly 4 percent Asian, and approximately 10 percent were of other racial ethnic groups. In Study 5A9908, conducted in Canada, a higher proportion of subjects, 86 percent, were Caucasian. Although not shown on this slide within the two control studies, demographic characteristics were similar for Pentacel and control subjects. And in the next few slides, I'll present data on serious adverse events from the pivotal studies.

This slide shows the percent of subjects with a serious adverse event within 30 days following any of doses one to three of study vaccines. Within the two control studies, 49401 and P3T06, the proportion of subjects reporting a serious adverse event was similar in the Pentacel and control groups.

Across studies, serious adverse events appear to occur at a lower frequency in Study 49401, approximately 1 percent of subjects, compared to the other studies; for example, approximately 3 to 4 percent in Study P3T06. Variability in exposures to childhood infectious diseases due to different geographic sites, as well as variability in proportions of subjects vaccinated during different seasons were offered by the applicant as possible explanations for this finding.

This slide shows the percent of subjects with a serious adverse event within 30 days following dose four of study vaccines. In the two controlled studies, the proportion of subjects reporting a serious adverse event was similar in the Pentacel and control groups, and as for doses one to three, serious adverse events post dose four appear to be less frequent in Study 49401 compared to the other studies.

This slide presents rates of serious adverse events that occurred in at least four subjects overall within 30 days following any of doses one to three of Pentacel or control vaccines. Now the control studies were not adequately powered to reliably evaluate differences between groups with

regard to particular serious adverse events, but the main purpose of this slide is to show the most frequently reported serious adverse events. Bronchiolitis was most frequently reported, followed by dehydration, pneumonia, and gastroenteritis.

This slide presents rates of serious adverse events that occurred in at least four subjects overall within 30 days following dose four of Pentacel or control vaccines. Dehydration was most frequently reported, followed by gastroenteritis, asthma, pneumonia.

As you've heard, a total of five deaths occurred during the pivotal studies, four among the roughly 6,000 subjects who received Pentacel, and one among approximately 1,500 subjects who received Daptacel. The deaths are listed according to the interval since the last dose of study vaccines. The causes of death in subjects who received Pentacel were asphyxia due to suffocation, head trauma, SIDS, and neuroblastoma. One control subject with ependymona died secondary to aspiration.

Given the historical association of wholesale Pertussis vaccines with acute encephalopathy, the two cases of encephalopathy identified in the pivotal studies deserve mention.

One case of ischemic encephalopathy was secondary to cardiac arrest following cardiac surgery one month after Pentacel, and the second was in a seven-week old infant who developed head lag, loss of visual following, and tremors eight days after Pentacel. Several café au lait spots were noted and an MRI showed left frontal horn enlargement and left frontal atrophy. The infant was eventually diagnosed with congenital encephalopathy. Information was not available on whether a more specific diagnosis was made. And given the historical concerns about neurological complications following pertussis vaccination and the causal relationship between wholesale DPT vaccines and febrile seizures, I'd like to take some time to present data on seizures from the pivotal studies.

First, I'd like to briefly review the use of antipyretics, which theoretically could affect rates of fever, febrile seizures, as well as some other solicited adverse events that I'll present later. For each of the first three doses, approximately 40 to 50 percent of subjects reported use of an antipyretic within three days following Pentacel or control vaccines. Approximately one-third reported use of an antipyretic within three

days following dose four, and in the control studies use of antipyretics was similar between vaccine groups.

This slide shows the number and percent of subjects who experienced a seizure within seven days following Pentacel or control vaccines. Pentacel subjects are pooled across studies, rates of febrile, afebrile, and possible seizures are presented following any of doses one to three, and following dose four. Overall, febrile seizures within seven days post vaccination were reported in four subjects, all post dose four, two out of roughly 700 HCPDT subjects, and two out of approximately 5,000 Pentacel subjects. Overall, there were three afebrile seizures within seven days post vaccination, one each following HCPDT, Daptacel, and Pentacel. There was one possible seizure within seven days following Pentacel in a subject who reported fever the same day.

Now for historical perspective, in the Sweden-I Efficacy Trial among approximately 26 infants who received Daptacel at two, four, and six months of age, there were two suspected seizures within seven days post vaccination, for a frequency of around 0.1 percent. And in the Sweden-II Efficacy

Trial, among approximately 20,000 infants who received HCPDT, usually at three, five, and twelve months there were four seizures within 48 hours for a rate of 0.02 percent.

This slide presents further available information on the febrile seizures, or possible febrile seizures that occurred within seven days post vaccination. Two occurred within three days post vaccination, concurrent illnesses noted included upper respiratory infection, viral illness, pharyngitis, all subjects recovered without sequella. And this slide provides further available information on the three afebrile seizures that occurred within seven days post vaccination. One subject experienced the onset of seizure activity the same day as the second dose of HCPDT. She had a recent history of an unspecified head injury, as well as a family history of seizures. Follow-up two and a half years after discontinuation from the study indicated continued seizure activity in that subject. One subject with an afebrile seizure six days following Pentacel went on to complete the study without further seizures, and one subject experienced a brief seizure associated with apnea on the same day as receipt of Daptacel.

Historical data have indicated a causal relationship between wholesale DTP vaccines and hypotonic/hyporesponsive episodes or HHEs, also referred to in the literature as collapse or shock-like states. Core systems of HHEs are sudden onset of pallor or cyanosis, limpness and hyporesponsiveness. While HHEs have been reported following a number of vaccines, most reports have involved Pertussis vaccines. In the pivotal studies, the HHE definition was an event of sudden onset within 48 hours of vaccination lasting one minute to 48 hours, involving limpness or hypotonia, hyporesponsiveness, and pallor or cyanosis, or failure to observe or recall skin coloration, and without known cause or urticaria.

In three studies during post vaccination phone calls, parents were asked about fainting or change in mental status, and in Study P3T06, the diary card included specific questions pertaining to the symptoms of HHEs. There were no reports of HHEs following roughly 17,000 doses of Pentacel, approximately 3,600 doses of HCPDT, or approximately 4,600 doses of Daptacel in any of the pivotal studies. One subject who received Daptacel reported an event that met the criteria for HHE, except that

it occurred 16 days post vaccination. Although differences in HHE definitions, as well as other factors, may affect observed rates of HHE, for historical perspective I would just mention that in the Sweden-II Efficacy Trial, the rate of HHE following HCPDT was 0.47 per thousand doses, and in the Sweden-I Efficacy Trial, there was one report of HHE following roughly 8,000 doses of Daptacel.

In the next several slides for the more commonly occurring solicited adverse events, I'll focus on the two controlled studies. Before presenting data on fever, I would like to review some information on routes of temperature measurement in the two controlled studies. Parents were instructed to measure temperatures rectally following the first three doses of study vaccines, and for the fourth dose, they were instructed to measure temperatures rectally in one study and axillary in the other. The actual routes used to measure temperature were recorded on the diary cards. Following each of the first three doses, approximately 45 percent of temperature measurements were axillary, and approximately 50 percent were rectal. In both studies following the fourth dose, roughly 60 to 70 percent of measurements were axillary, and

approximately 25 to 30 percent rectal. At each dose, the routes of temperature measurement were similar between the Pentacel and control groups.

Now in this slide and the next, the rates of fever are presented using the actual temperatures recorded without any adjustments for route of measurement. This slide presents rates of fever in Study P3T06 following doses one through four of Pentacel or U.S. licensed control vaccines. At each dose, subjects are categorized based on the highest temperature recorded over days zero to three post vaccination.

Although there appear to be some differences between groups and rates of fever at a particular dose, the rate of fever was not consistently higher in one group over the other across the four doses. In both groups, there was a tendency towards higher rates of fever with subsequent doses from dose one to three. For example, following doses one, two, and three of Pentacel, the respective rates of any fever were approximately 6, 11, and 16 percent. Because of the greater frequency of axillary measurements post dose four compared to dose one to three, it is difficult to interpret comparisons in fever rates following the

fourth dose relative to previous doses using the data presented here. The observations noted on fever in the previous slide also generally apply to the Pentacel and HCPDT groups in Study 49401 shown on this slide. And in the next slide, I'll show data on fever from this Pentacel group in Study 49401, stratified by route of temperature measurement.

So here Pentacel subjects only are stratified by two categories of temperature measurement route, rectal and axillary. And as explained in the footnote, at each dose these categories may not be mutually exclusive because approximately 5 percent of subjects switched route of measurement. For example, for a particular dose, a subject who had a rectal measurement on day one, and an axillary measurement on day three would be included in both categories on this slide. Nevertheless, I think these data illustrate two points. First, rates of fever greater than or equal to 38, as well as greater than 38.5 are generally higher when predominantly rectal measurements are used compared to axillary. For example, post dose three, any fever was reported in approximately 26 percent of subjects when predominantly rectal temperatures are considered compared to approximately

10 percent for axillary measurements. This difference is not apparent for fever greater than 39.5, although relatively few subjects reported this level of fever. And, second, using these data, it appears that the rates of fever post dose four are similar to or somewhat lower than those observed post dose three.

Now the data from the controlled studies did not raise concerns about increased rates of fever in infants who received Pentacel relative to separately administered control vaccines. However, because of the clinical importance of post vaccination fever in infants, I would like to note that in the pivotal studies, whether febrile infants had medical visits for fever was not specifically solicited or systematically assessed. Limitations in the ability to capture medically attended fever from the database include potentially missing non-hospitalized cases if they were not considered serious adverse events, and missing cases in which the actual reported diagnosis did not include the term fever. So, for example, an infant who underwent diagnostic studies to evaluate the cause of fever for whom the only reported diagnosis was viral illness may not be captured in an analysis of medically

attended fever.

This slide presents rates of selected systemic adverse events other than fever that occurred within three days following each dose of Pentacel or U.S. licensed control vaccines. Overall, the rates of decreased activity, inconsolable crying, and fussiness appeared generally comparable between the two groups. Each of these events were most frequent following the first dose, tended to decrease in frequency with subsequent doses.

This slide presents frequencies of solicited local adverse events at the Pentacel or Daptacel injection sites within three days following each of doses one to four in Study P3T06. The Daptacel injection site is being used as the comparator, as it is the more reactogenic of the separately administered control vaccines. Rates of local reactions were generally similar between the two groups. Each of these local reactions tended to be most frequently reported following the fourth dose of either Pentacel or Daptacel. For example, following Pentacel, redness was reported in seven to nine percent of subjects following the first three doses, and 17 percent after the fourth.

Next I'll review supportive safety data

from the post marketing use of Pentacel. As you've heard, Pentacel was first licensed in Canada in 1996, and is currently licensed in eight countries. Since 1997 to 1998, Pentacel at two, four, six, and 18 months, and DTaP-IPV at four to six years of age have been used exclusively in Canada to prevent pertussis, polio, and invasive Hib disease through early childhood. During the nine year period, May 1997 through April 2006, roughly 13-1/2 million doses of Pentacel were distributed, 92 percent of them in Canada. And to place the number of doses in perspective, I think it helps to note that the annual birth cohort in Canada is approximately 330,000.

During the nine-year surveillance system, Sanofi Pasteur received 288 reports of adverse events following Pentacel, predominantly from healthcare professionals and health authorities, with some reports from consumers and from published literature. Most events reported in the post marketing setting also have been reported in clinical trials of Pentacel. The most frequently reported events were injection site reactions or inflammation, fever, crying, and irritability. Under-reporting is a well recognized limitation of passive surveillance systems with serious life-threatening events and fatal cases

more likely to be reported than minor events. Thus, in the next few slides, I'll review post marketing spontaneous reports of deaths and encephalopathy following Pentacel.

During the nine year period, there were 14 post marketing reports of deaths. Shown here are five cases of SIDS, and four other deaths without known cause. All occurred between one and twenty-five days post vaccination, which is not surprising considering that events with shorter onset time after vaccination are more likely to be reported than those with a longer interval since vaccination.

Because of under-reporting, direct comparisons of passive surveillance data to population-based incidence rates is not entirely valid. Nonetheless, to place these data in perspective, I would like to note that the reported rate of SIDS in Canada in the late 1990s was one out of 2,000 live births each year, which would translate to approximately 170 cases per year. In the other five spontaneous reports of death, reported causes included Group B streptococcal sepsis, congenital anomalies, Hib meningitis following the first dose of Pentacel, and seizures.

During the nine-year surveillance period,

Sanofi Pasteur received three reports of events coded as encephalopathy following post marketing use of Pentacel. A fourth case of encephalopathy identified in a literature report was coded as convulsions, and a fifth case of encephalopathy identified in a post marketing safety survey conducted by the applicant in British Columbia also was presented in the BLA. For these five cases of encephalopathy, the time to onset of symptoms since the last dose was one, five, seven, ten, and twenty-four days respectively. In the first and third cases listed on the slide, influenza A virus was isolated from nasopharyngeal secretions, encephalopathy associated with influenza A infection previously has been described. The second case listed occurred in an infant with prominent bloody diarrhea, and one case was associated with atypical Kawasaki syndrome; finally, one was in an infant who presented with complex symptoms 24 days after vaccination.

Now in addition to spontaneous adverse event reports, the IMPACT system, which you've heard about, also provides information on the post marketing safety profile of Pentacel. Participating IMPACT hospitals, of which there are currently 12, encompass approximately 90 percent of Canada's

tertiary care pediatric beds serving an immediate population base of 3 million children, which is about half of Canada's population less than 15 years of age. The IMPACT centers also receive referrals from outside of the immediate catchment areas, and at the centers, all admissions for acute neurologic illness are screened for recent immunization.

This slide summarizes data from an IMPACT publication on encephalopathy that was included in the BLA. During the period 1993 to 2002, IMPACT centers identified three cases of encephalopathy or encephalitis within seven days after wholesale pertussis vaccine, and four after acellular pertussis. The ones after acellular pertussis included three after Pentacel, and one after the DTaP-IPV. Those following Pentacel were described in the earlier slide on post marketing cases of encephalopathy identified by the applicant.

One case following wholesale DTP had direct evidence of brain infection with herpes simplex virus, and other plausible causes, though not directly proven, were identified in each of the other cases. Considering the estimated number of doses of wholesale and acellular Pertussis vaccines administered to Canadian children during this period,

and the size of the immediate populations served by the IMPACT centers, the authors concluded that if any risk of developing encephalopathy or encephalitis exist as a result of vaccination, it would be less than one per 3 million doses of wholesale pertussis, and less than one per 3-1/2 million doses of acellular pertussis vaccine.

At IMPACT centers, active surveillance also was conducted to identify children hospitalized with seizures or HHEs, and children seen in emergency departments for HHEs. Immunization history was verified for identified cases meeting specified case definitions. Using Poisson regression models, average monthly admissions for seizures and reports of HHEs were compared between a wholesale DTP period, and the period when Pentacel was used. Between the two periods, hospitalizations for febrile seizures within 72 hours after pertussis vaccination decreased 79 percent, and reports of HHEs within 48 hours after pertussis vaccination decreased 60 percent.

In contrast, as a control analysis, admissions for febrile seizures within five to thirty days following MMR vaccine did not change significantly, so these data suggest a decreased risk for febrile seizures in HHEs with the introduction of

Pentacel in place of wholesale DTP vaccines in Canada.

So, to conclude, the safety of Pentacel was evaluated in a total of 5,980 subjects from four pivotal clinical studies, approximately 4,000 of these subjects were from studies of four consecutive doses of Pentacel, and approximately 1,800 were from a study that evaluated the fourth dose only. In two of the studies, Pentacel was compared to separately administered control vaccines, and in addition to the pivotal safety data, supportive post marketing safety data are available from a nine-year period in which approximately 13-1/2 million doses of Pentacel were distributed primarily in Canada.

This concludes my presentation, and next Dr. Theresa Finn will give FDA's presentation on immunogenicity of Pentacel.

DR. FINN: Okay. The efficacy of Pentacel will be inferred from the immunogenicity data, and Sanofi have presented Pertussis and haemophilus epidemiologic data from Canada. While these data can be considered supportive of efficacy, your consideration of the efficacy of Pentacel, which is the subject of the second question you'll be voting on, should be based primarily on the

immunogenicity data from the pivotal studies. Similarly, some of the data presented earlier today were the results of post hoc analyses using revised endpoints. Such post hoc analyses are of limited use to support regulatory decisions.

In my presentation, I will give a brief overview of the Pentacel studies pertinent to the evaluation of immunogenicity, and then I'll present the endpoints and data comparing the responses to diphtheria toxoid, tetanus toxoid, poliovirus, Hib components of Pentacel to those induced by the separately administered vaccines. Then I'll present the data to support the efficacy of the pertussis component.

First, a serology bridge to Daptacel in the Sweden-I Efficacy Trial, and then a comparison to Daptacel administered to U.S. children in a randomized study. I will finish with the data showing the response to the pertussis antigens when Prevnar is co-administered with Pentacel. In the interest of time, I will present only a summary of the concomitant vaccination data. The focus of my presentation will be on the pre-specified endpoints and analyses. Any exploratory analyses will be clearly identified, and my presentation will conclude

with a summary.

Data from two controlled studies in the U.S., Study 49401 and P3T06, will be presented. Details of these studies have been presented earlier, so I'm just going to highlight the comparator group relevant to the immunogenicity comparisons I will show later. In Study 49401, control subjects received separately administered HCPDT, which you've heard is the non-U.S. licensed formulation equivalent DTaP vaccine administered with Poliovax and ActHIB at two, four, six, and 15 months of age. This study was initiated before Prevnar became available; thus, approximately 80 percent of subjects received Prevnar concomitantly with Pentacel at two, four, and six months of age.

In Study P3T06, control subjects received Daptacel administered with IPOL and ActHIB at two, four, and six months of age. All subjects received Pentacel at two, four, and six months of age. For the fourth dose, those subjects who received Daptacel received other co-administered vaccines in a staggered fashion, and in my presentation I will focus on the immunogenicity data from the group that received the fourth dose of Pentacel concomitantly with ActHIB at 15 months of age, as compared to

Pentacel.

I am also going to present some immunogenicity from three additional Pentacel studies which did not include a group of subjects administered control vaccines, Study 49403 conducted in the U.S., in which subjects received four doses of Pentacel, and Canadian fourth dose study, 5A9908. Both of these studies have already been described. A summary of the post dose three immunogenicity data from Study M5A07, which was designed to assess whether co-administration of Prevnar with Pentacel interfered with the responses to the Pentacel antigens was included in the BLA, and this data will be presented.

The primary population for immunogenicity analyses was the per-protocol for immunogenicity population for each Pentacel study; that is, eligible vaccinated subjects who had blood draws and vaccines within specified windows and for whom serology data for at least one antigen were available. Post vaccination blood samples were taken approximately one month following administration of the third and fourth dose.

The immunogenicity of Pentacel was evaluated using non-inferiority comparisons for the

various antigens. At the time many of the studies in the Pentacel application were initiated, the protocol specified criteria for non-inferiority of GMC ratios and for differences in seroprotection and seroconversion rates were based on two-sited 90 percent confidence intervals. Currently, CBER recommends the use of two-sited 95 percent confidence intervals for these analyses.

At CBER's request, the manufacturer has provided all analyses using the 95 percent confidence interval. However, when I present the results of protocol specified non-inferiority analyses in my slides, I will use the protocol specified criteria.

The endpoints used to evaluate efficacy of the diphtheria, tetanus, polio, and Hib components of Pentacel are presented in this slide. For each of these antigens, there are accepted seroprotective antibody levels. For evaluation of the post dose three response to diphtheria, antitoxin levels of 01 international units per mil as measured by VERO as they were considered the minimum protective level. Antitetanus levels of 0.1 international unit per mil was measured by ELISA were considered the minimum protective level. Neutralizing antibodies to polio are recognized as conferring protection against

poliomyelitis, and antibody titers greater than a record of one to eight as measured in a neutralizing assay will be presented. Anti-PRP levels of 0.15 microgram per ml and 1 have been used as minimal and long-term protective levels respectively, and the applicant uses a radio-immuno assay to measure these antibodies. Anti-PRP GMCs will also be presented.

The next few slides will present the response to each of these antigens following three doses of Pentacel or control vaccines. When the results of analyses are similar between studies, I'm only going to present the data from one of the control studies, that's Study P3T06.

This slide presents the proportion of subjects with seroprotective levels to diphtheria and tetanus following three doses of Pentacel or Daptacel. One month following three doses of Pentacel or control vaccine, the response to these toxoids was comparable between groups, and approximately 100 percent of subjects had seroprotective levels of antibodies to both diphtheria and tetanus.

Similarly, the response to the polioviruses was comparable between groups. One month following three doses of Pentacel or separately

administered IPOL in Study P3T06, over 99 percent of subjects had seroprotective levels to each of the poliovirus types.

The following slides will present the immune response to the HIB component of Pentacel compared to separately administered ActHIB in both studies 49401 and P3T06. Data from both control studies will be presented, because these two studies showed inconsistent results with respect to Anti-PRP levels greater than or equal to 1 microgram per mil, and the geometric mean antibody concentration.

This slide presents the proportion of subjects with Anti-PRP levels greater than or equal to 0.15 and 1 microgram per mil, and the geometric mean antibody concentration one month following three doses of Pentacel or ActHIB in Study 49401. The last column in the table presents the results of pre-specified non-inferiority analyses. In this table, as in subsequent tables, the percent difference in rates is presented as the control minus Pentacel, and the ratio of antibody concentrations is presented as control antibody concentration divided by the Pentacel antibody concentration. For each comparison, the 90 percent confidence interval on the difference in the rate or the ratio is presented.

Non-inferiority is evaluated by looking at the upper bound on the confidence interval to see whether it is within the pre-specified margins. For example, 79 percent of Pentacel subjects had Anti-PRP levels greater than or equal to 1 microgram per mil, as compared to 89 percent of subjects who received ActHIB. The difference between these rates is 9.6 percent. And the upper limit of the 90 percent confidence interval on the difference is 12.9. Thus non-inferiority was not demonstrated for Anti-PRP levels greater than or equal to 1 microgram per mil, because 12.9 exceeds the pre-specified non-inferiority margin of less than 10 percent.

Similarly, the GMC to PRP following three doses of Pentacel is 3.2, as compared to 6.2 following three doses of ActHIB. The ratio of these GMCs is approximately 2, and the upper bound of the 90 percent confidence interval on this ratio is 2.26, which exceeds the pre-defined non-inferiority criterion of 1.5. Thus in this study, non-inferiority of Pentacel was not demonstrated.

The response to the PRPT component of Pentacel administered in Study P3T06 is shown in the next slide. In Study P3T06, 70 to 72 percent of subjects had anti-PRP levels greater than or equal to

1 microgram per mil one month following Pentacel or ActHIB. The GMC following three doses of Pentacel or ActHIB was 2.3. Thus in this study, unlike the observation in Study 49401, non-inferiority of Pentacel relative to ActHIB was demonstrated.

PRP antibody levels of 0.15 microgram per mil are considered protective levels. Thus an evaluation of the proportion of children with this level of antibody immediately prior to receipt of the fourth dose of Pentacel is an important measure of the longevity of protection following the third dose of conjugated polysaccharide vaccines. This slide presents the proportion of children enrolled in Study 49401 and P3T06 with anti-PRP levels greater than or equal to 0.15 microgram per mil at 15 months of age just prior to receipt of the fourth dose of either Pentacel or ActHIB.

Among Pentacel subjects here and here, 65 to 69 percent had protective levels of antibodies prior to receipt of the fourth dose. Eighty percent of those who received ActHIB in Study 49401 had seroprotective levels, as compared to 60 percent of ActHIB subjects in Study P3T06. These data suggest that the antibody level achieved following the third dose of conjugated polysaccharide influences the

proportion of subjects with protective levels at 15 months of age.

There is no generally accepted correlative protection for pertussis. Thus evaluation of the efficacy of the pertussis component of Pentacel was evaluated by comparing the immune response of Pentacel and Daptacel. The first comparison is a serology bridge in which the response to each pertussis antigen of Pentacel administered to U.S. children in Study 49401 was compared to the response to Daptacel in the Sweden-I Efficacy Trial.

The population of 49401 subjects used for this bridge included subjects who met the per-protocol for immunogenicity population, and had received concomitant Prevnar at two, four, and six months of age. The sera from Sweden-I were available stored sera which were re-assayed. The second evaluation was a comparison of the immune response to the pertussis antigens when Pentacel and Daptacel were administered to U.S. children in randomized Study P3T06.

I would like to point out that the analyses of non-inferiority using a revised definition of vaccine response as presented by Sanofi Pasteur have not been submitted to the BLA. Thus in

my presentation of the response to the pertussis antigens, I will focus on the pre-specified endpoints for evaluation of the response to each of the antigens. These pre-specified endpoints are the percent of subjects with a greater than or equal to four-fold rise in antibody level to each antigen relative to the pre-dose one antibody level, and the geometric mean antibody concentration to each antigen.

Before presenting the Pentacel immunogenicity comparisons, I will very briefly review the data from the Sweden-I Efficacy Trial, which supported licensure of Daptacel, and provide the rationale for the Pentacel comparisons I will present in later slides. I think this will address some of the questions that Dr. McInnes had earlier today.

The Sweden-I Efficacy Trial was conducted from 1992 to 1995. In this trial, efficacy of Daptacel was evaluated relative to a controlled DT vaccine. Approximately 2,500 infants received Daptacel administered at two, four, and six months of age. An efficacy against WHO defined pertussis was 85 percent, and the confidence interval was 80 to 89 percent. The pivotal data used to support efficacy

of Daptacel for U.S. licensure were the Sweden-I Efficacy Trial, and a serological bridge from Sweden-I to U.S. and Canadian infants. These data were included in the FDA briefing package, and are summarized in the next slide.

When the immune response of U.S. and Swedish infants administered three doses of Daptacel at two, four, and six months of age were compared, the anti-Pertactin seroconversion rates and GMCs were significantly lower in U.S. infants. The response to the other antigens was similar in U.S. and Swedish infants. The children in the U.S. study had not received a fourth dose of Daptacel. Therefore pertussis antibody levels of children who had received a fourth dose of Daptacel in a separate Canadian study were compared to the post dose three GMCs of the Swedish infants. In this comparison, the post dose four GMCs to all antigens, including Pertactin, were at least as high as those seen in Swedish infants. Based upon these data, four doses of Daptacel are considered the primary course for pertussis.

Since Pentacel contains the same quantity of Pertactin as Daptacel, it was expected that four doses of Pentacel would be needed to bridge to three

doses of Daptacel in Sweden-I. Thus to evaluate efficacy of the pertussis component, the immune response to four doses of Pentacel was compared to the response of Swedish infants administered three doses of Daptacel, and these data are shown in the next two slides.

I should point out, actually, that although Sanofi earlier presented a serologic bridge to P3T06, but the bridge to P3T06 is not included in the BLA, and has not been reviewed by FDA. Rather the BLA contains a comparison to Study 49401, and in my presentation I will show the serology bridge, as described in the BLA, and reviewed by FDA.

This slide presents a comparison of the GMCs following four doses of Pentacel in Study 49401, or three doses of Daptacel in Sweden-I. The comparisons were pre-specified, and non-inferiority criteria pre-defined. For all GMC comparisons, the upper limit of the 90 percent confidence interval for the ratio of GMCs was less than 1.5, the pre-defined limit for non-inferiority. However I'd like to point out that the upper limit on the 90 percent confidence interval for the Pertactin GMC is 1.49, close to the limit for non-inferiority. Using a 95 percent confidence interval on the ratio, the upper limit of

this confidence interval for Pertactin GMCs is 1.54.

The percent of subjects with a four-fold rise in antibody level to each pertussis antigen after three doses of Daptacel, or four doses of Pentacel, are shown in this slide. In each case, the fold rise post dose three or post dose four is relative to the pre-dose one level. The last column shows the results of the pre-specified non-inferiority comparisons. Although other pre-specified analyses that I presented used a 90 percent confidence interval, you'll note that in this comparison, non-inferiority was evaluated using increased specified 95 percent confidence interval.

Following four doses of Pentacel, the PT, FHA, and FIM seroconversion rates met the criteria for non-inferiority, because the upper limit of the 95 percent confidence interval was less than 10 percent. However non-inferiority was not demonstrated for anti-Pertactin seroconversion rates. The upper limit of the 95 percent confidence interval is 13 percent, which exceeds the pre-defined criterion of 10 percent.

Now the incidence of pertussis and its complications are greatest in children less than one year of age. Therefore I'm going to present an

exploratory comparison of the response to the pertussis antigens following three doses of Pentacel in Study 49401, and three doses of Daptacel in the Sweden-I efficacy trial. This comparison is analogous to that performed during licensure of Daptacel, which led to the post dose four comparison. So this slide presents CBER's exploratory analysis of the percent of subjects with a four-fold or greater rise in antibody levels relative to pre-dose one levels following three doses of Daptacel or Pentacel. The last column presents a difference in seroconversion rates, and the 95 percent confidence interval on this difference.

Similar to the observation during U.S. licensure of Daptacel, the Pertactin seroconversion rate following Pentacel is 95 percent, which is lower than that seen in the Sweden-I infants, which was 99 percent.

This slides presents the exploratory analysis of the post dose three GMCs of Swedish and U.S. infants to each of the pertussis antigens. The last column presents the ratio of the GMCs to each antigen. After three doses of Pentacel, the FIM GMC is 265, as compared to 340 following three doses of Daptacel in Sweden-I, and the upper limit on the

confidence interval is 1.58.

Following three doses of Daptacel in Sweden-I, the GMC to Pertactin is 111 ELISA units per ML, as compared to 38 following three doses of Pentacel. The ratio of these values presented in the last column is 3, and the upper bound of this confidence interval is 3.4. Together, these data suggest that following three doses of Pentacel, the immune response to Fimbriae and Pertactin may be diminished, as compared to three doses of Daptacel in Sweden-I.

Next I'm going to present the immune response to each of the pertussis antigens in Pentacel, as compared to those following administration of Daptacel. Study P3T06 was a randomized study conducted in the U.S., in which subjects received Pentacel, or separately administered vaccines, including Daptacel. All subjects in Study P3T06 received Prevnar concomitantly with either control vaccines, or Pentacel at two, four, and six months of age. Non-inferiority was evaluated following the third and fourth dose of each vaccine. Following three doses of Daptacel or Pentacel, the percent of subjects with four-fold or greater rise to each pertussis antigen

met the pre-defined criteria for non-inferiority. The upper bound of the 90 percent confidence interval was less than 10 percent for each comparison.

Similarly, in a comparison of GMCs post dose three, the upper bound of the 90 percent confidence interval for the ratio of GMCs was less than 1.5 for each antigen. Thus non-inferiority was demonstrated. Following four doses of each vaccine in Study P3T06, non-inferiority of seroconversion rates was demonstrated for each antigen. However four doses of Pentacel were inferior to four doses of Daptacel with respect to Pertactin GMCs. Following four doses of Pentacel, the GMC was 94 ELISA units per ML, as compared to 186 following Daptacel. The upper limit of the 90 percent confidence interval is 2.25, exceeding the pre-specified criterion for non-inferiority, which is 1.5.

Historically, a diminished response to the pertussis antigens has been noted when Prevnar was administered with some DTaP vaccines. In Study 49401, Prevnar was introduced after the study had initiated, and prospectively specified exploratory analyses of data from this study suggested that co-administration of Prevnar with Pentacel or control vaccine may interfere with the post dose three and

four response to the pertussis antigens. Also suggestive of interference of Prevnar with the response to the pertussis antigens was the available post dose four data from the Pentacel pivotal studies, and these results are shown on the next slide, these data.

So this slide shows the GMCs to each of the pertussis antigens following four doses of Pentacel in pivotal studies 5A9908, 49401, P3T06, and 49403. The number of doses of Prevnar co-administered with each dose at two, four, six, and 15 months is indicated. Study 5A9908, which was conducted in Canada before Prevnar was used, so no Prevnar is administered. In Study 49401, subjects may have received zero to three doses of co-administered Prevnar. In Study P3T06 and 49403, all subjects received Prevnar with Pentacel for the first three doses. However subjects in Study 49403 were randomized to receive the fourth dose of Prevnar either separately or concomitantly. All assays were performed in the same laboratory during a period when assays were demonstrated to be stable over time. And if you compare the GMCs within each row, the data suggests that the responses to each of the antigens are lower in the U.S. studies, as compared to Study

5A9908, which was conducted in Canada. For example, the response to the fimbriae in Study 5A9908 is 833 ELISA units per mil, as compared to 324 in Study 49403, when four doses of Prevnar were co-administered. Similarly, the response to Pertactin as seen in 5A9908 is 187 ELISA units per mil, as compared to 69 in Study 49403 in the group three that received all Prevnar.

These types of cross-study comparisons should be interpreted with caution, and I have presented this particular slide relative to Prevnar as the variable, but alternatively, these data may suggest that either a population difference exists, or that the response to the pertussis antigens is variable, or has changed over time.

To evaluate whether Prevnar did indeed interfere with the response to pertussis antigens, Sanofi Pasteur initiated Study M5A07. And Study M5A07 was designed to prospectively evaluate immunogenicity of Pentacel when administered with four doses of Prevnar, or administered Pentacel at two, four, six, and 15 months, and Prevnar at three, five, seven, and 12 months of age. The BLA contains a summary table with post dose four data. The next two slides present these post dose three summary data

for each of the antigens.

This slide presents the pertussis seroconversion rates one month following administration of the third dose of Pentacel in Study M5A07. In the second column are the data for the group that received Pentacel with Prevnar, and the third column presents seroconversion rates for the group of subjects that received staggered Prevnar. Following three doses of Pentacel, either administered with Prevnar, or one month apart, the percent of subjects with a four-fold rise to each antigen met the pre-defined non-inferiority criteria. Similarly, co-administration of Prevnar does not appear to interfere with the GMC following three doses of Pentacel. Post dose four data from Study M5A07 have not been submitted to the BLA.

As noted earlier by Dr. Decker, Sanofi have submitted these post dose four data to the IND. They were submitted yesterday and received at 5:30 p.m.

As I mentioned in the outline of my presentation, I will not present detailed data showing the response to other recommended vaccines when co-administered with Pentacel. These data have, however, been included in your briefing document,

and the conclusions are summarized in this slide.

In the two control studies, 49401 and P3T06, children received the second and third dose of Hepatitis B vaccine co-administered with Pentacel at two and six months of age. Within each of these studies, the response to Hepatitis B was similar when administered with Pentacel or control vaccines. In Study P3T06, Prevnar was co-administered with Pentacel or control vaccines. In this study, the proportion of subjects with antibody levels greater than or equal to 0.15 microgram per mil, and greater than or equal to 0.5 micrograms per mil to each serotype was similar between Pentacel and control groups, as was the GMC to each serotype. In Study 49403, the response to the fourth dose of Prevnar when given with Pentacel at 15 months of age was non-inferior to the response to the fourth dose of Prevnar given with MMR and Varivax at 15 months. Study 49403 also evaluated the response to the first dose of MMR and Varivax when administered with Pentacel or Prevnar at 15 months of age. In this study, non-inferiority was demonstrated for seroresponse rates to each antigen.

My next two slides summarize the concerns arising from evaluation of the immunogenicity data.

This slide summarizes the results and concerns regarding the immune response to the PRPT component. The response to PRPT was variable. In one control study, Pentacel was inferior to ActHIB control with respect to seroprotective levels greater than or equal to 1 microgram per mil and GMC. In the other control study, the proportion of subjects with anti-PRP antibody levels greater than or equal to 1 microgram per mil, and the GMCs were similar following Pentacel or the ActHIB control.

The concerns with regard to the response to the pertussis component of Pentacel are summarized in this slide. In an exploratory analysis, the response to the FIM and Pertactin antigens appeared lowered following three doses of Pentacel, as compared to the response in the Sweden-I study. Following four doses, and although a diminished response to Pertactin was perhaps expected based on data during licensure of Daptacel, the diminished response to the fimbrial component was not expected. Following four doses of Pentacel in either the serology bridge to Sweden-I, or within Study P3T06, the response to Pertactin was inferior to that following Daptacel.

And that concludes my presentation. My

next three slides present the voting and discussion items, but if you have any questions for clarification, I'm happy to address them.

CHAIR KARRON: Thank you, Dr. Finn. Are there questions for Dr. Finn or Dr. Farizo? Dr. Larussa.

DR. LARUSSA: A question about the safety data on slide 34, where you go over the redness and swelling after the fourth dose. The category is greater than 50 millimeters, and the percents are 2.3 and 0.8 percent. Do we actually have numbers of how large they were?

DR. FABRIZO: We did get those in the BLA. I'm sorry, I don't have those with me for those few subjects who had greater than 50 millimeters.

DR. LARUSSA: Do you remember your impression, huge, small?

DR. FABRIZO: You know, I think there -- I don't know for -- I can't remember. I can say that looking at the actual sizes did not raise concerns, comparing the Pentacel to the DTaP separately administered injection arm.

CHAIR KARRON: Dr. Butler.

DR. BUTLER: Thank you. Question for Dr. Finn. When comparing Pentacel to ActHIB, were there

differences in the PRP responses to dose one and two?

DR. FINN: That was not evaluated.

CHAIR KARRON: I think if there are no other questions for the FDA at this point, we'll move on to the open public hearing.

MS. WALSH: As part of the FDA Advisory Committee meeting procedure, we are required to hold an open public hearing for those members of the public who are not on the agenda, and would like to make a statement concerning matters pending before the committee. I have received one written comment from B. Sachau. A copy of this statement has been given to the committee members, a copy has been placed in the viewing notebook at the registration desk, and a copy of this statement will be made part of the official meeting record. Is there anyone in the room who would like to address the committee at this time? Dr. Karron, I see no response. I turn the meeting back over to you.

CHAIR KARRON: We're now at the time in the meeting for committee discussion prior to the re-presentation of the questions. I know that there were several questions raised by members that we thought might be better explored during this longer discussion, so we're ready to proceed. Dr. Self.

DR. SELF: I have two questions. The first is regarding the diminished response to Pertactin. That seems very clear, but I'm struggling a bit with how to interpret that, because responses to the other antibodies were deemed not inferior, or perhaps even a little bit better. The only information that you gave in the presentation was on slide 8, I believe, that showed a table that began to describe joint effects of antibody responses on protective efficacy, but really not to the level of detail that is useful in trying to interpret the impact of this response profile on protection, so I'm wondering if you could provide a little more information about that.

CHAIR KARRON: Are you asking that question of the sponsor, who provided the table?

DR. DECKER: I have to remember to turn the microphone on. Excuse me. Indeed, let me lay the groundwork. Let me explain what lies behind that study, which I know you know, because you wrote about it, but others may not, and show you those details you're asking for. Could I have Slide SB106 on, and then we'll go through that sequence.

First of all, let me tell you a little bit more about Sweden-I, because you need to know a

little bit more in order to understand this. As I mentioned in my original presentation, this was a multi-vaccine efficacy trial sponsored by NIH. It compared Daptacel, it also included a two-component acellular pertussis vaccine from Belgium that did not perform well, and was not further developed, and never licensed anywhere. It included a U.S. licensed wholesale vaccine that was in widespread U.S. use, and it included a Swedish DT vaccine, as the placebo control.

The Swedish investigators designed prospectively a household contact study that they intended to nest within this efficacy trial, and in support of that household contact study, they arranged for a periodic phlebotomy of the children so that they would have a reference serum specimen prior to any possible infection. Next slide, please. So ultimately, they had 329 enrolled children who were exposed in this household contact study. And after you take out those who didn't get all their vaccine, or for whom sera were inadequate or unavailable, we're left with 209 to form the basis for the regression analyses that the investigators performed to try to identify serological correlates of protection. Next slide, please.

Now Storsaeter and her colleagues reported that as they worked through their various regression models, they found that their most parsimonious and effective model was one in which they dichotomized serum antibody levels to what were reported in the table we showed you before, one of their summary tables, as low or high. What that really means is that persons with fewer than five ELISA units per ML, less than five ELISA units per ML of antibody to a given antigen were categorized as low. If you had five or more, you were categorized as high. They found that to be the most predictive break point. They found that higher antibody levels did not confer increased protection. So for example, if one child had 100 units, one child had 50, one child had 10, they all seemed to be equally well protected. If you fell below five, you lost your protection.

There was no influence on the regression model by vaccine group affiliation, which is a very important outcome, because these vaccines differed strikingly in their overall efficacies. But it didn't matter which vaccine you got. What mattered was how much antibody you got, a very important result. And antibody to PT correlated only with

protection against typical pertussis; that is, a WHO defined classic whooping cough. And that finding from the Storsaeter study has been supported by multiple other studies. For example, there's a one-component vaccine, PT only, that was licensed in the U.S., and licensed in Europe, no longer available in the U.S., but it was used for many years in some European countries, and demonstrated good control of classic pertussis, but not good control of mild disease. Storsaeter and her colleagues found that the anti-TRN and the anti-FIM antibodies correlated with protection not only against typical, but also against mild disease, which makes sense, because those are attachment proteins, and antibodies there may interfere with the attachment of the organism with human respiratory epithelium. Next slide, please. So this is a slide that Dr. Kuykens showed earlier. Next slide. And this is a revision of it, replacing those categorical labels with actual numbers. So to restate what was said earlier, if you have at least five units of antibody PT, no matter what you have for FIM or Pertactin, you've got 46 percent efficacy, 46 percent protection against invasive pertussis disease.

No matter what your PT level is, and even

if you have no Pertactin antibody, as long as you've got at least five units of FIM, you have 72 percent protection. No matter what your PT antibody is, and even if you have no FIM, as long as you've got at least five units of Pertactin, you've got 75 percent protection. And no matter what your PT antibody is, if you've got five units of both FIM and Pertactin, your efficacy is 85 percent. Next slide, please.

So Kohberger and colleagues recently presented a new model that stands entirely on the Storsaeter model. They used the Storsaeter regression model, and they applied that model to the actual antibody levels observed in our pivotal trials P3T06 and 49401. So we've got three columns here, the Pentacel recipients in P3T06, the Pentacel in 49401 -- I'm sorry, I said that in the reverse order -- and the Daptacel recipients, which of course, is only P3T06. And shown are the Kohberger projections of actual in-use efficacy for Pentacel, or for Daptacel post dose three, post dose four, and pre-dose five. And you see they're very comparable and quite high. Next slide, please.

Now FDA mentioned in their briefing document and presentation another efficacy trial, the Sweden-II trial. After the Sweden-I trial was

running, the NIH and the Swedish investigators collaborated to execute another efficacy trial in Sweden that differed from the Sweden-I trial that you've heard a lot about in a couple of important ways. The first is that several of the vaccines were changed. Instead of Daptacel, the DTaP components of Pentacel, so Pentacel without the IPOL and HIB, IPV and HIB, were used for one of the vaccine arms.

Concurrently with Sweden-I, NIH was executing an efficacy trial in Italy of very similar design that incorporated two three-component vaccines, the Biocine Italian three-component vaccine, and the Belgian three-component that's used in this country as Infanrix. In the Italian efficacy trial, those two vaccines had identical efficacies of 84 percent. In order to provide a bridge to that trial, NIH and the investigators brought one of those two vaccines, they happened to choose the Italian one, up to Italy and made that a second arm of the study. A third arm of the study was the Belgian two-component vaccine, which because results were not yet broken, they did not know was not performing well, and so it continued for the first part of the Sweden-II trial. And then, finally, the U.S. wholesale vaccine performed poorly in Sweden-I. They replaced

it with a known high-efficacy European vaccine, the British Wellcome vaccine, so that's one change.

The other very important change in the study design was rather than immunizing the kids primarily at two, four, six, the U.S. schedule, they immunized them at three, five, twelve, which is the standard schedule used then and used now in Scandinavia. The Scandinavians believe they've had a more effective program by giving a two-dose primary series at three and five, and a booster at 12 months of age, so that's what the overwhelming majority of these kids received. The surveillance case definition was a WHO definition, as in the prior study.

Now surveillance for pertussis was ongoing throughout the period of the trial. And most particularly, surveillance was ongoing between that five month dose, and the 12 month dose, a fairly substantial period of time, seven months, in which there were numerous cases of pertussis. And so the Swedes calculated and published efficacy results for the period of time following two doses. Next slide, please. So arrayed on this slide we have the various antigens and the reported efficacies reported by the investigators, and then the antibody levels. The

first column is the antibody levels as calculated by us in the bridging study in our laboratory from the Sweden-I sera, the sera that were provided to us out of Sweden-I. The second column is the post dose four antibody results from P3T06. The third column is the post dose four antibody results from 49401, and the last column is the antibody levels the Swedish children had following two doses in Sweden-I at five months of age.

Now between the second dose in Sweden-I and the third dose in Sweden-I, during that seven month period that Dr. Finn commented was a particularly critical period, the efficacy based on those antibody levels of Pentacel was 82 percent. The antibody levels post dose four in P3T06 and 49401 dwarfed the antibody levels that were necessary to have 82 percent efficacy in Sweden-II. Next slide, please. And relevant to the question that was asked by Dr. McInnes earlier, the post dose three antibody levels from P3T06 and 49401 also are substantially higher than the levels seen following two doses in Sweden-II. The Pertactin levels are the ones that are lowest, as everybody has noticed, but they're still higher than the levels associated with 82 percent efficacy in Sweden-II.

Now how does this all make sense? It all makes sense because of what the Storsaeter model tells us. The critical question appears to be, based on the best available data for this vaccine, not how high is the highest -- how high is the GMC, but rather, what proportion of the kids have more than five for these critical antigens? Next slide, please. There's one more slide of this. Could I have the summary slide summarizing the four critical points, please. Slide on, please. So one of the two questions that's been laid in front of you as a critical question is, will this vaccine work against pertussis? And there are four separate and independent lines of evidence that this vaccine will have high efficacy against pertussis.

First, the Pentacel GMTs in both P3T06 and 49401 were non-inferior to Sweden-I for all pertussis antigens, including Pertactin. So if you want to stand just entirely within the pre-defined correlates and the clinical trials, non-inferiority was met for all four antigens in both clinical trials. If you want to look at the body of evidence outside that, the antibody levels in P3T06 and 49401 were far above the Storsaeter cutoff for high, and the Kohberger analysis showed Pentacel and Daptacel

efficacies to be identical. P3T06 and 49401 antibody levels post dose three, as well as post dose four, far exceed the levels associated with 82 percent efficacy in Sweden-II. They're similar but higher for Pertactin, they're much higher for the other three antigens.

There's a reason why this is a five-component vaccine. All five components contribute to protective efficacy. The Pertactin results are lower, the other antibody levels are higher, the vaccine provides equal protection. And then, finally, I'm not sure if VRBPAC has ever before been in the happy situation of having a vaccine come forward for U.S. licensure that has a decade of real world experience in a relevant neighboring country, so there's a fourth independent line of evidence to support the efficacy.

DR. SELF: What's the model base prediction of efficacy for the Sweden-II profile of responses?

DR. DECKER: Say again, please.

DR. SELF: What does the model predict the efficacy would be given the Sweden-II study profile --

DR. DECKER: I'm looking at Bob, and he's

shaking his head. I think that means he didn't run that. It's a great question, and I wish we'd thought of it. And speaking of wishes, I want to apologize to Dr. Finn for her getting data that she and we both wish were available two months ago to her last night, but trying to empty the bucket and get everything to everybody that we can.

DR. SELF: So I have one more question about the HIB, and that is, I was not sure what your explanation was of the failure to show non-inferiority of the antibody response. Are you suggesting that it was a failure of randomization, or is there something more going on, referring to variability across sites, and across time, and across trials? Could you explain that a little bit more?

DR. DECKER: Yes. You're referring to 49401, and the simple answer is, we don't know what happened. If I'm going to be strictly scientific, the only conclusion I can make is that if some country wanted to license and give as separate components HCPDT, Poliovax, and ActHIB, they could achieve HIB antibody levels twice as high as anybody is achieving now with any currently used regimen anywhere in the world, but I don't believe that, given my experience over the years. What I believe

is that if we redid that same study two or three times, we wouldn't get the same result, but we don't have that. This is the only time that particular combination has ever been looked at, so what I rely on in bringing Pentacel to you is the P3T06 data. What we know is that ActHIB is the dominant vaccine used in the United States. The HIB performance of Pentacel is identical to the HIB performance of Daptacel, IPOL, and ActHIB given as separate vaccines, and that's what's done predominantly in the U.S. right now.

We have excellent control of HIB right now, and will have excellent control of HIB using Pentacel. And we get reassurance of that by looking at, again, the Canadian data. But we not only meet non-inferiority, we have identicality with P3T06 for the HIB results all across the board.

DR. SELF: So for HIB, you're really relying most heavily on the epidemiologic data from Canada.

DR. DECKER: Personally, I rely most heavily on the head-to-head comparison to the U.S. We're not in the situation right now of the country is using HCPDT, Poliovax, and ActHIB separately, and we're proposing replacing it with something that

produces only half the antibody. If that were the situation, there would be a serious question here, but that's not the situation. The country is using Daptacel, IPOL, and ActHIB separately, and Pentacel, as you saw in P3T06, is identical. Nobody in the world uses that other triad as separate vaccines, so we have no other experience to compare that to, so I rest predominantly within our clinical trials on P3T06 with respect to HIB. But I draw great reassurance from the real world experience of the decade of Pentacel's use in Canada, where HIB is controlled -- I mean, the most sensitive indicator for HIB disease is the native population, and in that circumpolar surveillance we see that the attack rate for HIB in the Pentacel recipients is essentially the same. Actually, it's a hair lower, but of course, the numbers are so small there's no significant difference. Can I have that circumpolar surveillance slide on, please? That's not the circumpolar surveillance slide. Out of the core presentation, the circumpolar surveillance slide. Thank you. Slide on, please.

So you notice out of 137,000 total population in Canada, there was one case in the non-native population, and three cases in the native.

Similarly, in Alaska, 664,000 total population, but in the non-native, one case. In the natives, the other six cases. Three out of 75,000 is a lower rate than six out of 120,000, probably no significant difference. I'll assume they're the same. I'm happy that it's lower, and so the Canadian data give us great confidence on the real world performance of Pentacel in a population that's more highly biased towards the high-risk group, than the U.S. P3T06 tells us the Pentacel will perform identically with respect to HIB, as does the current U.S. standard of care.

CHAIR KARRON: Dr. Butler.

DR. BUTLER: Mike, since the circumpolar slide keeps coming back up, what's the time frame for these data?

DR. DECKER: Slide on, please.

DR. BUTLER: Because they don't seem to jive with Singleton's report in pediatrics this summer, which shows three cases of invasive HIB disease in Alaska natives since 2001.

DR. DECKER: We had to make a decision about what would be the best comparative time frame. And so as you see, the years don't match, but there's a reason for that. The data from Canada

represent the five years of available data for Pentacel use. The period for the U.S. is shifted because from 2000 to 2002, there were several vaccines used in Canada, and you have to worry about vaccine effect. The first five years in which the only vaccine used was OMP was the 2002 to 2006 period, so we selected that as being the least biased comparator. David, do you have another comment, because this is your slide?

DR. GREENBERG: Jerry, I just want to comment to you that with the additional help of your colleagues, I was able to extend the data in the Singleton report. So you remember the Singleton report correctly. I followed it up, the cases that occurred prior to 2002 were six doses that occurred in 2000. I chose not to show those six cases on this slide because those included some children who received an initial dose of PRP-OMP, and then subsequent doses of HbOC, so to be fair, I showed on this slide only the cases after PRP-OMP as a single vaccine was instituted in Alaska. So I tried to be as conservative as I could, but extended the data so that we would have comparable five year surveillance periods between Alaska and the polar regions of Canada.

DR. BUTLER: I guess I'm concerned that this is showing that four cases in 2006, which doesn't quite sound right with me. But I don't have the data right in front of me.

DR. GREENBERG: Could I have the slide of the cases in -- the Slide MS13, I believe it would be, the cases. Can you go to the next slide, please?

DR. DECKER: While David is getting that, while the team is finding the slide that shows the actual cases, let me just comment -- since OMP is considered classically the standard of care vaccine for high-risk populations, we also thought that comparing only to it was the most conservative comparison. We didn't want the question of if we're comparing to a period with multiple vaccines, what does it mean? Could we see for a moment the slide -- we're going to come back to this -- is MS11 the one you want?

DR. GREENBERG: No, it's a table that shows each of the individual cases from Alaska.

DR. DECKER: Could I have MS12 up on the screen while you're looking for the table that David wants. So you know this inside out, but others here don't, so that the world can see what we're talking

about. Here's the sequence of vaccine use in Canada, I mean, I'm sorry, in Alaska, and so that second row represents the period that we thought was the most fair to compare to. It's a five year period with only one vaccine used, and the vaccine used was considered the standard of care. Is this the slide you want?

DR. GREENBERG: Yes, please. Could you show that slide up? So again, with additional help from your staff, we have the six cases in 2000. Some of them received zero, one, or two doses, given three doses of HIB vaccine. The first dose would have been PRP-OMP, but subsequent doses were probably HbOC. Then the cases that you remember are 2002, 2003, and `04, and those were the three cases that are in the Singleton report. Then, subsequently, there were three cases in `05, and a case in `06, and all of those -- one of them received no doses, but three had received three doses, and that should be with PRP-OMP, since that's what's been used since 2001.

DR. BUTLER: Okay.

CHAIR KARRON: Dr. Jackson.

DR. JACKSON: I just wonder if you could fill in some of the missing data for the bridging comparisons, specifically looking at the GMCs. You

know, we've been told that for the primary analysis of comparison with 49401, the non-inferiority analysis was borderline with an upper confidence limit at 1.49 using a 90 percent confidence interval, and 1.54 using 95. Then in the Sanofi documents, there was a sub-analysis presented, which was mashed in order to alleviate some of the differences in baseline antibody, and we were shown the four-fold rise data, but not the GMC data for that analysis, so I wondered if those data were available? And then the second bridging comparison involved P3T06, and we were shown a figure, but not numeric data for the confidence intervals around the estimates of non-inferiority for the GMC comparison of the P3T06 with the Sweden-I study, and I wondered if it would be possible to see those data.

DR. DECKER: Yes. I'm not sure, honestly, that I follow all that, so if I get it wrong, you steer me back in the right direction. Okay? Do we have -- for the P3T06 bridge to efficacy, instead of the figure that shows -- well, let's put this up for starters. All right. But I think we're asking for a table of the 90 percent confidence limit. Could I have Slide SP135 on the screen, please. All right.

Let's start with this, and then using this, tell me where you want me to go. This is a summary slide. You haven't seen it before, as such, but you've seen every element in it before. This summarizes on one slide the GMC comparisons between Pentacel and Sweden-I. The top half is for P3T06, the bottom half is for 49401. As you've heard me allude before, I'm not a big fan of four-fold rise. I don't think it tells us anything really about the performance of the vaccine, or whether it's protecting the population. I think the critical measure, personally, is the antibody level you achieve by vaccination, and we've looked at that several ways. If we stand within the clinical trials and look only at the pre-specified endpoints, you're looking at them right here, and all are met for GMC. A number of four-fold rise endpoints were not met because of higher pretiter. I think this might be -- what was asked? Could I have LC15 up, please.

Now here is P3T06 versus Sweden-I with actual, not a figure like that, but the actual numerical results. Is this one of the things that you wanted to see?

DR. JACKSON: Right. So it appears that the upper limit of the confidence interval crosses

the 1.5 barrier, if I'm interpreting that correctly.

DR. DECKER: Right. It's Pertactin. Pertactin crossed -- if we look at the confidence limits, we've got -- had it been pre-defined, we would be claiming superiority for PT, superiority for FHA, failure for Pertactin, superiority for FIM.

DR. JACKSON: Unless I'm mistaken, it doesn't appear to match with your previous figure.

DR. DECKER: Well, these are 95 percent.

DR. JACKSON: Okay.

DR. DECKER: And the figure, the pre-defined was 90 percent.

DR. JACKSON: I see.

DR. DECKER: And for those -- if there's anybody who gets confused by all these confidence limits, you can pre-define any confidence limit you want. And if you make the study big enough, you ought to hit it. But once you establish a confidence limit, like a 90, you design the study to be large enough to meet that confidence limit. If you then come back later with a higher confidence limit, you're likely to fail because you didn't have enough bodies. If the world says it wants 99 percent confidence limits, that can be done, but the studies will cost ten times as much because you have to have

ten times as many people to shrink the confidence limits.

DR. JACKSON: Of course, with these bridging studies, your sample size was pre-determined. You weren't at liberty to set the sample size.

DR. DECKER: Well, that's part of the problem because on the -- you know, we can set the sample size on the U.S. side, but we're handed the sera from Sweden, and that's all we have. And it turns out -- it's a very good point, because it turns out that the limit -- help me, please -- the absolute limit on the power for Pertactin was what -- we talked about this. Our sample size, no matter how we enlarged the sample size, the power for Pertactin on the bridge is limited because of the inherent variability in the Pertactin samples from Sweden and their small number. I'm sorry, the guys aren't thinking of the number, but it's something we looked at, because we wondered could we make this stronger by having more bodies. The answer is no. We're just totally strapped by what Sweden-I gave us.

DR. JACKSON: Right. So then my last question involved the sub-analysis, the match analysis you did, in which we were presented the data

on the four-fold rise, but not the data on the GMC comparisons, in that sub-analysis.

DR. DECKER: I think that the team worked up some slides on that, so I'm looking at them, hopefully, to see what they'll show me.

DR. JACKSON: Okay.

DR. DECKER: Does your matching analysis help with that, Fernando? The matching analysis of -- when you did the matching analysis, did you calculate GMCs, as well as the four-fold rise results?

I'll repeat. All right. But I don't think that would get what we want. I don't know that we have exactly what you want. Could we put up Slide SP17, please. This goes at the part that you've already seen. It's just the numbers behind what I said before. It didn't occur to us to do what you're asking for, in part, probably because of the way that I looked at this, which is that the GMCs speak for themselves. All right? Taking the study group as a whole, those endpoints were met. The question arises with the four-fold rise, and why was that not met when GMC was, so we looked at that, and we saw the difference in the pre-titers, and we looked to see whether that difference that we could see in the

distribution pre-titers explained it, and it did, and we stopped there.

DR. JACKSON: I guess I don't think that the -- it's firmly established that the criteria for non-inferiority were met with GMCs, given that it was borderline for 49401, with a 90 percent, and did not achieve non-inferiority with a 95, and the data you just showed us for P3T06, in which you chose a 95 percent limit, did not meet those criteria also, so that's why I'm interested in looking at the GMCs for the analysis that may have corrected for some of the difference in baseline, which should not be as influential for GMC measure as for a four-fold rise measure, I agree.

DR. DECKER: Could we have this slide on, please, SP23. I'm not sure this goes directly to what you're asking for either, but if you divide the population at a pre-titer of 20, these are the GMTs you get. Those who did not have a pre-titer higher than 20 have a GMT of 88, those who did have a pre-titer of 20 or higher, all of whom, or most of whom failed four-fold rise, because they started high, but nonetheless, they had a GMT of 144, so they did quite well, even though they failed four-fold rise.

DR. JACKSON: Right. But in that same

group, the Daptacel percent was 98.7, I believe.

DR. DECKER: I'm sorry?

DR. JACKSON: Well, you're only --

DR. DECKER: Slide on again, please.

DR. JACKSON: This is the data for only the Pertactin, only for the Pentacel group, and similar data were presented, also restricting the Sweden-I group to those with titer less than 20, or the --

DR. DECKER: There was only one case.

DR. JACKSON: There was only one case that was higher than 20.

DR. DECKER: It was only one kid, so it would have had --

DR. JACKSON: So it's still 98 --

DR. DECKER: Yes, it would have had a negligible impact.

DR. JACKSON: Yes.

CHAIR KARRON: Actually, just a follow-up question about that. Does the FDA have data -- I seem to remember from their briefing document that looked at this issue of stratification by pre-antibody, and looked at GMCs across between Sweden and the Pentacel groups. I think it's Table 15 in your briefing document.

DR. DECKER: Are you looking at Table 15 in the FDA briefing document? Could we have that slide on, please?

DR. FINN: Thank you. I didn't realize that you put up our briefing document to slides. Yes, this is basically expansion of the slide that Dr. Decker just showed where you can see that -- well, this was actually an analysis that was presented in the BLA, in which the pre-dose one titers were stratified by whether you were less than 20, or greater than or equal to 20, and other antigens were done, but this presents just the anti-Pertactin response. And you can see that if you just take the group who had pre-dose one antibody levels of less than 20, that those in Sweden-I who received three doses of Daptacel, the GMC was 111, as compared to 88.3 in the group that received four doses of Pentacel in 49401, so I would imagine that that would fail a non-inferiority bridge for GMCs.

And as Dr. Decker just pointed out, there was only one subject in Sweden-I who had a titer greater than or equal to 20 prior to vaccination, and that individual had a GMC of 100. There were 28 individuals in the Pentacel group who had a pre-vaccination greater than or equal to 20 ELISA units

per mil, and of those 28 individuals, the GMC was 144.43. I mean, this was actually presented in the BLA to support the contention that if you start out with a high pre-vaccination titer, you may have less a percentage of folks, of subjects showing a four-fold rise. But I think if you look at the GMCs, you can see that even in the -- if you break it out like these, even those with a pre-vaccination less than 20, the GMC is lower than the same comparator group in the Daptacel Sweden-I Study.

DR. JACKSON: I don't want to belabor it, but it's just -- there could be some variability, even among the less than 20 group, and so that's why it was interesting to note that the Sanofi study apparently matched more closely. We weren't given a lot of information about those methods, and probably had less variability, even among the lower end of the group, and so that's why I was interested in the GMCs in that group.

DR. DECKER: Maybe I can follow up on that a little bit more and give you some more information, because there's -- could I have the slide on, please? In the primary presentation, you saw this slide. And you may have noticed that unlike the other three --well, let me first tell you what

this is, again. This is the RCD curve, Pentacel post dose four, versus Sweden-I. The heavy white line is the Pertactin curve from Sweden-I, and the thin lines are all the various Pentacel trial curves. And unlike PT, FHA, and FIM, here the shape of the Pertactin curve in Sweden-I doesn't match the shape of the Pertactin curve from Pentacel. And I don't know if you noticed that when it went by, but I sure noticed that when I had time to pore over this, and I wondered what was going on, because I expect the curves to match in shape. Well, it's an interesting story. Next slide, please.

The Swedes bled 181 kids. That represents their ITT population for serology. A hundred and seventy-eight kids were in their PP, their per-protocol population, and those 178 formed the basis for all the serological reports coming out of the Swedish investigators for the Sweden-1 efficacy trial. After they were through, there were 129 subjects who had sufficient sera to ship to us from the Swedes' point of view, but when the sera got to us, we found serum for only 84 kids, and so when we came to you in 2000 for the licensure of Daptacel, the bridge to efficacy that we presented at that time was based on a sample of 84 sera. In conducting

those assays, we exhausted the sera for four kids, so when we came to you in 2005 for the licensure of Adacel, that serological bridge to efficacy was based on a sample of 80 remaining sera from Sweden-I. And we did the Pentacel trials were bridged at the same time, so it's the same 80. So a very fair question is, an important question is, are the 80 representative of the 181, because it's the antibody distribution in the 181 that's our best reflection of what it takes to get 85 percent efficacy in the Swedish population. Next slide, please. And so the Swedes, of course, had all 181. If we go to the Swedish laboratory and we look at their assay for the 181, versus their assay for the 80, we find that it's essentially identical for PT, essentially identical for FHA, essentially identical for FIM. But by happenstance, the GMT of the 80 for Pertactin is materially higher than the GMT for the 181 for Pertactin. So the official bridge that we have to rest on for our bridge to efficacy is representative of Sweden-I for three of the four antigens, but it's biased in that we're meeting an artificially high standard for Pertactin. So one of the questions that we had -- next slide, please. And not only is it a shift in the GMT, the whole curve is shift. The

white curve is the Swedish lab's assay of the 80, that's the reference we've got to beat. The yellow curve is the actual Swedish lab's assay for the 181, so that's why the curve is not the same shape for Sweden-I Pertactin as it is for the Pentacel studies. Next slide, please.

I want to remind you again, bridging to the official bridging sample of 80, we meet non-inferiority for all four antigens for both pivotal trials, but had we had the full 181, we can calculate how it would have looked. Next slide, please. Just a simple ratio, if the 80 in Sweden's hands was 129, and the 181 in their hands was 110, then when the 80 are re-assayed in our lab, they're a 111, that reflects inter-lab variation, 129 to 111. That's why we do a bridge. Next slide, please. We can calculate by ratio that had we had the full 181, our best estimate is that the bridge number we would have had to meet would have been a 95, not a 110. So what would that mean, how would we look then? Next slide, please.

And I'm making FDA crazy, because this is all conjectural and post hoc, but I'm just showing you everything I have. All right. On the right you see the 111.3, which is the official bridge number.

Next to it, the 95.1, which is our best effort to calculate what it should have been had they not used up so much serum. The horizontal white line is at the 95.1, and shown to the left in blue is every single one of the U.S. licensure trials for Pentacel, Pertactin, GMTs. So I think this is relevant, but I'm strongly comforted by the fact that if you hold your vision strictly to the pre-defined criteria for non-inferiority, we meet it, even with the official bridge of 80.

CHAIR KARRON: Dr. Hewlett.

DR. HEWLETT: May I ask a couple of procedural things? You said that you got those sera and did the assays, and then you just showed the curve of the data, the Swedish data. You have their data, individualized data?

DR. DECKER: We have for each individual in their study, their antibody results, as run in their lab. We have the antibody results for the same people as run in our lab, only for the people for whom there was enough sera.

DR. HEWLETT: Right. And how did those match up, because you're -- the difference you're showing is comparing the whole group to your 80, their data. And just a procedural thing; obviously,

this --

DR. DECKER: Slide on, please.

DR. HEWLETT: Pertactin is one of the antigens that has been shown to have micro heterogeneity, and I just wondered which Pertactin you assayed, and whether yours was the same as the one they used.

DR. DECKER: Let me do that second, because I can't do that, so I've got to let the guy who can do that think about it. I showed you before the table, so I won't repeat that. The table that I showed before where I filled in the fourth cell in yellow, that's the table that tells you numerically how the Swedish GMC compares to our GMC. All right? So you've seen that. You're asking for more, so here's the RCD curve.

Now both lines are Swedish numbers. The heavy line is the official reference. I'm sorry, I said that wrong. That's not what this slide is. Let me back up. Both lines are the 80. The heavy line is the Sweden assay of the 80, the thin line is our assay of the 80, so that's how our assay differs from the Swedish assay. I think those are reversed, aren't they, Jim Melochen? Since our numbers are lower than Swedes', aren't the labels reversed on

this? I'm going to assume they are until contradicted, because we know that the Sanofi Lab assay produces a numerically smaller number than the Swedish Lab assay; therefore, I think the numbers are --

PARTICIPANT: He says yours is the thicker line.

DR. DECKER: Oh, yes, I'm sorry. I'm just misreading it. Thank you. I apologize. All right.

DR. HEWLETT: Okay. So you are assaying Pertactin using the same antigen as they used?

DR. DECKER: Tim, do you know the answer to that?

DR. HEWLETT: So you're showing that there is a difference. On those 80, there is a difference between your assay and their assay.

DR. DECKER: Yes. And there's a difference for all four antigens because they're different labs. Tim, do you know the technical detail on the Pertactin assay?

Do you happen to know -- this is a long time back and I don't know, Bruce might remember. He's here in the audience somewhere. Bruce, who supplied the antigen to Sweden for their assay?

DR. MEADE: At this point I don't recall, and I'll keep thinking and see if I can come up with an answer.

DR. DECKER: Erik, there's three possibilities. We might have, we supply antigen to a lot of people for assay. GSK might have, they were in the study also, or it might have been FDA antigen. We just don't know right now.

DR. HEWLETT: And I think this is before there was the level of recognition now of the heterogeneity that occurs, that has been recognized. At least the initial analysis of these may have been done prior, so I don't know that the attention was being paid at the time to which antigen was which. Bruce may know that also. And I need to ask Bruce another question. If I understand correctly, you're making a comparison between the numbers in the Swedish study in which the stratification above and below 5EU, ELISA Units, and you're comparing those to your ELISA Units. And I want to know -- I want to make sure I understand correctly whether that's appropriate to do.

DR. DECKER: Wait a minute. That's not what I've done right now. You're harking back to earlier.

DR. HEWLETT: Yes, you said that --

DR. DECKER: No, early --

DR. HEWLETT: -- below five is way down here, and your numbers are all the way up here.

DR. DECKER: All right. But I think I can answer that directly for you. For simplicity, we just took the Storsaeter five as five. We didn't recalculate. The difference -- could I have back up the slide that's the two-by-two table that shows -- that has the yellow 95 in it? Okay. Let's put the numbers up, so we see what we're looking at. And this is just Pertactin, but it's representative of the others. Slide on, please.

So in Sweden for the 80, 129, 111, those are hard facts, we know that. Okay? So we've got what, approximately a 10 percent difference in the two labs, so if we had gone through and tried to correct that five, we're talking 4.5 versus 5, or 5.5 versus 5, but our antibody levels are 50s, and 100s, and 300s, so we just didn't bother making that correction.

DR. HEWLETT: No, I understand. But I just want to make sure that -- if I understand correctly from Bruce, that it's fair to compare your 50 and 100, and over 100 to those five, above and

below five.

DR. DECKER: Oh, yes. We're way closer than that.

DR. HEWLETT: Okay.

DR. MEADE: I mean, what I can say with -- for this case with certainty is that the Swedish lab did calibrate their assays against the CBER references, so that the -- and I believe, and I'll let the Sanofi lab - I think they also calibrated, it's the same reference.

DR. DECKER: Slide on, please.

DR. MEADE: So I believe both assays were calibrated with the same calibrator.

DR. DECKER: Erik, there's a concordance curve.

DR. MEADE: The numbers would be relatively similar, should be. But obviously, they could qualify that more clear.

DR. DECKER: Sorry, Bruce. Erik, here's the concordance curve between the two labs. So as you see, there's a 10 percent difference, but they correlate very closely.

DR. HEWLETT: Thank you.

CHAIR KARRON: I would actually like to go back to the HIB titers. And I'm struggling a bit

with the difference between the two studies, P3T06 and 49401, not the difference in the levels of antibody --is it on now? I just hate to turn my back.

DR. DECKER: It's on now.

CHAIR KARRON: Okay. Not the difference in the antibodies induced by Pentacel, which are actually not that great, but the differences in antibodies observed following ActHIB in those two studies. And I was just wondering if you could, because you, obviously, by now have a lot of experience with ActHIB. If you could put the titers that were achieved in each of those studies in the context of other studies of ActHIB, so that we can understand are the titers seen in P3T06 artificially low, are the titers seen in 49401 artificially high, how do they fall in the context of other studies of ActHIB?

DR. DECKER: Slide on, please. I think the best answer to that is to show you a slide that I showed you before, but directly attending to your question here. Here you have in chronological sequence all of the studies for Pentacel done in the U.S. and Canada. Pentacel on the left, and control groups, if any, on the right arranged in chronological sequence, so P3T06 numerically happens

to be among the lowest. As I showed you, there's substantial variability in HIB results.

M5A03 and M5A07, which are the next two after that, are done in the same population. I mean, P3T06, M5A03, and M5A07 are all contemporaneous studies done in U.S. populations at multiple study sites, so this is another indication of the variability we're seeing right now.

You know, there's two issues going on here, because there's a historical issue. If you could pull out a ActHIB package insert, or anybody else's package insert from the original licensures, which they all still have the same numbers from the original licensures, as far as I know, you're going to see numbers that look a lot higher, but those were with wholesale, OPV, no IPV, no Prevnar, none of these other things going on, at a time when the assays may not have been as well calibrated, and typically in very small groups. For example, the studies that Dave Greenberg and I did back in the mid-80s of these vaccines, we were happy to have 100 people in the study, but those sites that I showed you in P3T06 with that enormous site-to-site variation, those sites had 100 people, so it's very risky to compare both across time and to other

studies, especially with HIB.

Now the three right-most blue bars there, actually, all five starting -- everything from 49401 on, are reasonably contemporaneous studies, all done in a comparable population, and that's the amount of variation we get, all done in the U.S., all done in U.S. kids, all done in the last few years, and all done with something pretty close to, if not exactly, the current recommendation, the current U.S. schedule, so that's the inherent variability.

I think the only way to know for sure what's going on with a question like this, you have to have a large enough study -- I mean, we've seen that you'll go astray if you don't have a big study with multiple sites across the country, and if you're not comparing head-to-head randomized within each center, the same -- your two questions. You can't compare across time, across centers, or across studies. You're just going to go astray.

CHAIR KARRON: So just -- in some ways, the answer to the question is yes and yes, that P3T06 is unusually low, and 49401 is unusually high in the range of what you're seeing.

DR. DECKER: Yes, for the control group. And for 49401, what we don't know is whether there's

some interaction going on. We know from other studies that concomitantly administered separate vaccines can interact with each other. Since nobody else has ever looked at these three given concomitantly, we don't know if there's an interaction that's artificially -- not artificially, but unusually raised the HIB response. We don't know.

CHAIR KARRON: Dr. McInnes.

DR. McINNES: Michael, I wanted to go back to the question of the post fourth dose and the post third dose in Sweden, because it's the timing issue that I'd like to explore a little bit. So if we think about the kinetics of the response to haemophilus and PRP, as well as to the pertussis antigens, and we start off normally with the low dose, by six months of age when we're post second dose, pre-third dose, we've got a nice response normally. And then when we look again at seven months of age, we continue to increase. By the time we look at 15 months of age, or seven, whenever the booster is going to be, we've dropped back down to somewhere between what the level is around between the first and the second dose.

DR. DECKER: Are you talking about HIB,

Pam, or pertussis?

DR. McINNES: No, I'm including the pertussis.

DR. DECKER: So it's a global comment now.

DR. McINNES: In this broad sweep now.

DR. DECKER: Okay.

DR. McINNES: And then we give the fourth dose, and we normally are rewarded with this wonderful rise in antibody. So when I hear about the comparisons being post fourth dose in 17 month old infants, compare bridging to Sweden post third dose in seven month old infants, I'm tossed back to thinking about the times when we look, when we had to actually move up the fourth dose of HIB-OMP, and you remember it well, it went to a 12 month boost, because we were not sure we were going to be able to sustain antibody levels. And in fact, we saw them falling off, and so that was moved up. So I'm wondering, and if you put together the Sweden-II data with the three, five, 12 regimen; and yes, it was post second dose, but that seven month gap to the 12 months of age, and there were pertussis cases in there, and so I'm sort of trying to put all of this together and think about that space between the third

dose and the fourth dose in our immunization regimen being from when we would normally measure seven months of age to the same, we've got 10 intervening months in there. What do we know -- do we know anything about that kinetics, and in broad scope across all of your studies? And I'm thinking about still your bridge to efficacy in Sweden-I at seven months of age.

DR. DECKER: The slide on, please. I'm thinking of several ways to get at what you're asking, so let me try this. If it doesn't work, you redirect me. You saw this slide before. I think this gives some insight into what you're asking. Could I first have the -- no, this is good. Stay with this one, and then we'll do 113 after this one. Okay.

The Sweden-I official bridging antibody levels are shown in that first numerical column. The Sweden-II actual antibody levels after the dose given at five months of age is shown in the right-most column. And in between, you've got the post dose three, P3T06 and 49401 results. So if I heard right, I heard several questions embedded. One question is seeking further reassurance that -- well, let me back it up one step. Part of the question I hear is, why

on earth are we bridging fourth dose, when we're worried about kids after their third dose? And the answer to that, in part, is a regulatory answer. Because that was the basis of licensure for Daptacel, and this is a follow-on to Daptacel, we're following that method. So okay, that's fine. That answers the regulatory question, but then there's the clinical question. Okay. But what about the kids after the third dose, are they really okay? And that's why this slide is so important, because this directly addresses that, and it gives you very strong reassurance based on real world data that there's more than enough antibody after the third dose of Pentacel to provide at least 82 percent protection, as measured by the Swedes. And so we also have the Storsaeter model, and the Kohberger model that has projections directly onto our data, but those are models. And all of us love models, but we don't fully trust models.

This is real world numbers of real kids who are out there being monitored for pertussis, so this validates the Storsaeter and Kohberger models, and I think gives you that reassurance you're seeking.

Now the second part of your question was,

what do the antibody levels look like between the third dose and the fourth dose? Now we may have this on a single slide somewhere else, and I'm thinking of mine, but I know I have it right here, so if you'll just look at those middle two columns, and try and remember what they look like, and let's go to slide 113. And you see they more or less double, so when you give the kid the fourth dose, you do get that kick in antibody that you wanted.

DR. McINNES: What does it look like right pre-fourth dose?

DR. DECKER: We have a slide of that, don't we, pre-fourth dose P3T06 and 49401 antibody levels? I think we have that. Just give us a second. This is one of your slides, right? I don't have the power to project that onto the screen, somebody else has to make that happen. Thank you. All right. It's up on the screen. This is from the FDA presentation; meanwhile, team, you can continue to look and see if we have similar data. I have to familiarize myself with the layout for a second.

So pre-dose four, Pentacel PTs are about 11, Daptacel is about 8, FHA PTS are 11 to 13, for Pentacel, Daptacel is 5, FIM is 36ish, Daptacel is 29, Pertactin is seven six, and it's seven eight for

Daptacel. So Pentacel compares very favorably pre-dose four to Daptacel, about equal or a little lower for Pertactin, better for the other three. I have never seen anything that doesn't make me think that kids given Pentacel will be protected at least as well as kids given Daptacel.

CHAIR KARRON: Dr. Farley.

DR. FARLEY: I have a couple of more questions about the HIB issue, and knowing we're not going to solve the discrepancy between the two studies, but is -- given the fact that we have some possibility that the immune response might be a little bit lower with this compared to giving it separately, we do gain a lot of benefit from herd immunity and the issue with the conjugate polysaccharide vaccine that we reduce carriage, and that's been established nicely. Do you have any information on whether we're going to give anything up with Pentacel in terms of the effect on carriage, and the benefit of herd immunity?

DR. DECKER: No direct data. I have two ways to address that. One is, I can show you data from outside the U.S. that may help on that. We have no direct data. The other thing that's worth mentioning is that we've already been in discussion

with colleagues at CDC, Nancy, Sonya and others about what type of surveillance we might coordinate on if and when Pentacel is licensed, because clearly that's something that needs to be done. And given the rarity of HIB disease, and the difficulty of monitoring pertussis disease in the United States, this can only be done with a national program. So one of the things that we intend to do is to try to coordinate on this, both for HIB, you've got the ABCs, Active Bacterial Core Surveillance Program, which is an excellent source. I'm confident that will give us HIB monitoring post Pentacel, so that's easy.

Pertussis is a lot tougher, and there are several things that we can look at. We can look at household contact studies. We can look at studies in states that have good active vaccine registries so that we can actually know what vaccines the kids got. We can also look at studies that are done in the half a dozen or so states that are universal purchase states, so that you can be confident that everybody under the study got the same vaccine. We can look at that. The other thing that can be looked at is carriage studies to see if anything is going on with that. But all this is in the future. It's being

talked about, but there's no way to do it right now. To the best of our knowledge, and Scott -- you can stay there, because I think the answer is no. Are you aware of any carriage study in Canada post Pentacel?

DR. HALPERIN: No.

DR. DECKER: No, so that's it. Now something else that gives some insight into this though, I think, is the comparative HIB data from around the world. In Germany where you saw data already, they administered the vaccines that are scheduled very similar to ours, three, four, five, and a second year life, midyear booster is the most typical schedule. And for a long time, as I think Dr. Greenberg showed you with his slide, they began introducing Multivalent combination vaccines about a decade ago, and progressively gone from two component, to three component, four component, five component, six component vaccines. A number of the vaccines that they are using are known to have substantial interference with HIB, such that your HIB levels comparing the actual separate vaccines to the combined one are reduced 50 to 75 percent. And yet, Germany's got no increase in HIB disease.

Other countries that have not used a

U.S.-like schedule, when they have gone to interfering HIB vaccines, have seen an increase in HIB disease, countries that don't use a second year life booster. So the second year life booster appears to be important in providing you assurance that whatever vaccine you use, you have no recurrence of HIB disease. And in the United Kingdom, for example, they have recently instituted nationwide use of Pediocel, which is the same as Pentacel, except a different presentation. And they've added to that, to their traditional two, three, four month schedule with no booster, they've added a HIB booster in the second year of life in order to control their HIB issue. So we all would like to know what the results are of carriage studies, but what's important to know on a programmatic basis is that we've got the right schedule. If we hold to it, you're not going to have any problems. Nobody else in the world with a schedule like ours has ever had any problems, only those who don't give a booster in the second year of life.

CHAIR KARRON: Dr. Royal.

DR. ROYAL: Thank you. I've been trying to think back to slides, I believe shown by the FDA detailing the racial distribution in some of the

cohorts, and I have to wonder if you've had a chance to look at some of the immunogenicity data in those cohorts, and whether there may be some concerns for any specific groups.

DR. DECKER: I think you'll be pleased with the answer, Dr. Royal. Could I have the ICD curve showing the immunogenicity by racial group? Slide on. What they happened to find first was HIB. It's an analogous answer for pertussis. This is just the one they happened to find first, and if you're looking for the pertussis, I'll want to see that also.

Shown in the heavy white line is the standard of care, P3T06 as a whole, the aggregate of population. Shown in the big colored lines here are Pentacel results, but unlike all the other slides I've shown you like this, in this case, the different lines are not different studies. The different lines are -- each line is all studies combined, one racial group, so you've got Caucasian, black, Hispanic, Asian, and other. The lowest -- the GMTs that are most southwest are Caucasian. All the minority groups have, on average, higher GMTs than the Caucasians. Black is the gold line which is intertwined here with the other line, and then

further to the northeast on the slide is the Hispanics and the Asians. And this fits exactly with what's already known, people who have been doing HIB studies know that if you want to see high HIB numbers, do a study in Latin America, or in Asia. I don't know why, but you get HIB numbers through the roof, so this correlates exactly with what's already known. The overall average is shown, but every identifiable minority group is served well by the vaccine. Could I have the next slide on, please? And what came up first, PT. Okay. So you see exactly the same thing for pertussis antibody responses. The P3T06 is shown in the heavy white line, Caucasian is the next line to the right, and then the other racial groups are further to the right, even higher than Caucasians.

CHAIR KARRON: Dr. Larussa.

DR. LARUSSA: So could we go back to the age-specific rates of pertussis in Canada? I think that's C131. So let me ask my question while this is coming up. Looking at the antibody titers is reassuring, but I'm still a little worried about the point that Dr. McInnes is bringing up concerning the gap in the first year of life, and when you look at that curve, it looks almost like there's starting to

be an increase in the less than one year age group. Can you tell me a little bit more about that? Is that real or are the numbers so small?

DR. GREENBERG: What we've seen in Canada as we've gone over time is that we're seeing a higher proportion of cases under one year of age, but particularly under six months of age where they have either been unimmunized or haven't completed their course, so most of those cases in that -- I apologize, I'm color-blind, so I'll point -- in that line, are in the under six months of age, so they're not vaccine failures.

When we've actually looked at the change in incidence, we're seeing our best control, the most substantial drop is in the six month to 18 month age group. And I should say that again, as more reassurance that we don't give our vaccine at 12 to 15 months of age, we give it at 18 months of age, so even with a three-month longer gap, that's still the area we're getting our best control of pertussis, so whatever the antibody levels are, the effectiveness of this vaccine is fine up until that booster, and then we get another nice control up to five years of age.

DR. DECKER: Well, let me comment also,

that the recent increase in cases under one year of age seen in Canada, as Melinda can confirm, is exactly what's being seen in the U.S., and it's believed that this is predominantly below six months of age, and the thinking of a lot of people is it reflects the extraordinary rise in pertussis among adolescents and young adults, the parents, and so on, which Adacel and Boostrix is intended to attack that issue. But the U.S. and the Canadian epi look identical in this regard.

CHAIR KARRON: Dr. Hetherington.

DR. HETHERINGTON: A question at the other end of the age spectrum. What do we know about the persistence of antibody in the Canadian experience with this vaccine? And is there any potential knock-on effect for adolescent vaccines later on?

DR. GREENBERG: In Canada, what we saw was a cohort effect, a marching cohort effect of increased incidents in older children, and that was primarily related to the wholesale vaccine that we've been using a decade before. We don't have data on how -- what we see, though, as we've had five doses of Pentacel vaccine, that eight is moving out, so that before we initially had -- what we initially had

was a peak around eight or nine years of age, the next year it was nine, 10, 11, 12, so we just get a moving cohort out. And that's been seen elsewhere, as well, so we're giving Adacel at 15 years of age. We suspect that a 10-year gap will be fine. After a wholesale vaccine, we actually -- the ideal time to have given a booster probably would have been about eight or nine years of age, but with Pentacel, we're seeing a longer duration of protection now into mid-adolescence. We don't know if that would last even longer. We suspect that 10 years is about the right time.

CHAIR KARRON: Are there -- yes.

DR. SELF: One last question. What do you think the most important issues are going to be if you get to a post marketing situation? And do you have a set of studies that you're considering to be that program that you could share?

DR. DECKER: Well, as far as studies that we, ourselves, would execute entirely within our own resources, what we're presuming right now is that we'll be asked to do exactly the same type of post marketing safety study for rare adverse events that was conducted post licensure of Menactra and post licensure of Adacel. And for those that don't know

what that was, we're talking about -- I'm going to make something up now, because we haven't talked about this with CBER yet. But I wouldn't be surprised if we didn't end up doing something like finding a large automated records institution, such as Kaiser, having Pentacel become the base vaccine used there, and then analyzing all data collected for over a period, such as a year, which would give many, many, many thousands, hundreds of thousands of doses under analysis, and then conduct analyses looking for rates of rare events, and comparing them to historical standards, or looking at self-control intervals, such as the 30 days, first 30 days, versus the next 30 days following vaccination, something like that, to see if there are any signals of a problem. This would be a typical post licensure commitment, and analogous to what we've done previously with Menactra and Adacel.

I think, to me, as an epidemiologist and a clinician, the really interesting questions are ones that we cannot address as a company, but we may be able to coordinate with CDC to help ensure they address it. We may be able to provide resources, ideas, something else, collaborate to make sure it happens.

I have been wanting for a decade to know how the -- we have five licensed acellular vaccines in this country, three are still marketed. Anybody know how they compare? We've got a population of 300 million, and we don't know how they compare. And the reason we don't is because the way we deliver vaccines in this country, you don't know what anybody got for sure, except in rare circumstances, so we're very dependent on having highly accurate functioning vaccine registries to try to even do those types of analyses, and CDC has been handicapped, thus far, by the absence of those. Any study that doesn't have that is quite difficult to pull off, but we're progressing on the vaccine registries, and I think we're probably getting to a point where we could really start looking at that question, which is one that everybody is interested in. So that's something I'm eager to talk with CDC about.

And then the other thing I already mentioned is, obviously, if we're going to make a major change in our HIB vaccine, we're going to have close surveillance for what's going on in HIB afterwards, and that's going to be best done through the ABC's Active Surveillance System, where we have a very well-described and stable database. We've got

reference populations and good surveillance, so that's what I see.

CHAIR KARRON: Dr. Hewlett.

DR. HEWLETT: Mike, you have provided a number of explanations for the apparent differences in the Pertactin immunogenicity, and I wonder if you are sufficiently, I'll say this in a loaded way, sufficiently interested or concerned about that that that's something that you would follow-up in post licensure utilization to see whether it's a real phenomenon or not, whether something needs to be done about it.

DR. DECKER: In a sense, no, but let me explain why. I don't think that the variation in response to the individual antigens is really that important. It's the aggregate performance of those antigens that really matters, and there is some interesting scientific issues here. But in terms of either corporate or national responsibility to follow-up what's going on, the real question is disease occurrence on the impact on that. So I suspect that most of the resources that are looking at effectiveness are going to be looking at the occurrence of disease, and not monitoring things, such as how antibody level may vary between the

antigens, because ultimately, who cares, if the disease is gone.

DR. LARUSSA: Well, let me make one -- for the sake of argument, one point about why you might care. And we're going to have probably more combination vaccines in the future, and it certainly would be useful to understand what happens to immunogenicity when you start throwing more stuff in the vial. Now some of the explanations you've given could be taken to mean you don't really think there's a difference in immunogenicity because of the differences in study design and how the assays were measured. But if you do think that there's a difference in immunogenicity, then I would say you should go after that and figure out what's going on.

DR. DECKER: Well, with respect to the first part of what you raise, the prospects for the future, and more combinations over the next decade and two coming forward, which everybody expects -- pretty much where we still stand right now is that a pertussis -- a DTaP vaccine, a pertussis vaccine, will have to stand on its efficacy trial. I don't see any pertussis vaccines coming forward that have not had efficacy trials. There were nine or ten efficacy trials conducted, and they pretty much cover

the gamut of all the manufacturers, and all the vaccines that have any viable contention of being in a combo. I think what we're going to see is that they all licensed based on bridge to efficacy, and comparison to the current standard of care.

If somebody actually came up with a novel acellular pertussis vaccine, this would be a very difficult challenge for CBER and the scientific community because at present, the scientific literature gives you no confidence that you can project the results for one vaccine onto another vaccine, even if you know the components. As you know, I've been writing what I'm about to say for a decade, my chapters on this -- I firmly believe that the performance of an acellular pertussis vaccine is based on three things; the number of antigens, but that's not determinative. We've seen one-component vaccines work well. The amount of each antigen, but that's not determinative, because we've seen, particularly for the PT component, how you make the antigen. And I don't know how you abstract those from the real efficacy trial, turn them into numbers that you can apply to a new vaccine that's never been studied in an efficacy trial. So I mean, that would be a very desirable goal. I just don't know how

we'll be able to do that. And I don't think it actually matters, because I'm not aware that there's any candidate anywhere in the wings that isn't based on an already efficacy trialed-based vaccine.

DR. SELF: Isn't this exactly what you've done with the modeling effort and arguing that the profile of antibodies and titers greater than five have latent efficacy?

DR. DECKER: That all flows out -- all these data come from the same vaccine. We're not using a different efficacy trial for a different vaccine as the basis. The five-component vaccine was in that efficacy trial, and that's where we're getting those numbers. Now it may turn out, as I'm sure you know, in one of the German efficacy trials, Jim Cherry and colleagues tried to do the same work, but we don't know whether the results were fully extrapolable, because the vaccines they happened to use in that trial were not well-representative of the currently available vaccines. Neither vaccine that was in that trial is marketed any more, and the four-component vaccine that was in that trial is technically a four-component, but it's almost purely an FHA vaccine, with a small amount of PT, and negligible amounts of Pertactin and FIM, and so the

regression analyses are very weak on those questions. That's just where it is right now.

CHAIR KARRON: Yes, Bruce.

DR. GELLIN: It might be -- you've highlighted and the others have highlighted that we're in a different position here because we have -- as Scott showed us, we have significant experience in Canada to help us with our decision today. I think the flip side of that coin is really one other question about -- a corporate question of why now? We get lots of questions -- I get lots of questions about the status of the vaccine market in the United States, so I'm curious to know what the thinking is about the timing of bringing this vaccine to us now, and to the United States market now, particularly given the history. And as David reinforced, the ACIP and others' recommendations about the value of combination vaccines programmatically.

DR. DECKER: Long before I joined this company, I was wishing for this vaccine in the U.S., and wondering why not then, why is it taking so long? The file that we submitted to CBER in support of this license is, I believe, and CBER can correct me if I'm wrong, but I believe it's the largest electronic file they ever received for any vaccine.

The number of studies and the amount of data is enormous. Licensure in the United States is the top of the mountain, and it takes a lot of time to climb there. I wish we'd had it five years ago.

CHAIR KARRON: Any other comments or questions from committee members? Okay. Hearing none, I think we will proceed to our voting on questions. Could we have those projected, please? Okay. The first question is, are the available data adequate to support the safety of four doses of Pentacel administered at two, four, six, and 15 to 18 months of age? And if the available data are not adequate, what additional data are needed? Dr. Farley, we're going to begin with you.

DR. FARLEY: I'll vote yes on this first question.

CHAIR KARRON: Thank you. Dr. Butler.

DR. BUTLER: Vote yes.

CHAIR KARRON: Dr. Larussa.

DR. LARUSSA: I'll vote yes.

CHAIR KARRON: Dr. Wharton.

DR. WHARTON: Yes.

CHAIR KARRON: Dr. Self.

DR. SELF: Yes.

CHAIR KARRON: Dr. Hetherington.

DR. HETHERINGTON: Yes.

CHAIR KARRON: I'm sorry. Industry opinion doesn't count.

(Laughter.)

CHAIR KARRON: But thank you. Sorry. Dr. Word.

DR. WORD: Yes.

CHAIR KARRON: Dr. Jackson.

DR. JACKSON: Yes.

CHAIR KARRON: Dr. Gellin.

DR. GELLIN: Yes.

CHAIR KARRON: Ms. Province.

MS. PROVINCE: Yes.

CHAIR KARRON: Dr. Stapleton.

DR. STAPLETON: Yes.

CHAIR KARRON: Dr. Royal.

DR. ROYAL: Yes.

CHAIR KARRON: Dr. McInnes.

DR. McINNES: Yes.

CHAIR KARRON: Dr. Hewlett.

DR. HEWLETT: Yes.

CHAIR KARRON: Dr. Modlin.

DR. MODLIN: Yes.

CHAIR KARRON: And I also vote yes. Okay. The second question is -- the question is

really, are the available data adequate to support the efficacy of Pentacel? And in your response, you're asked to consider the diphtheria, Tetanus, and polio components, the HIB component, and the pertussis component. So this time, Dr. Modlin, we're going to start with you.

DR. MODLIN: I think we did a very thorough job of dissecting the Pertactin issue. At the end of the day, I do believe what's real important here is where this vaccine will prevent young infants from being hospitalized with pertussis and reduced morbidity and mortality. And even though there may be some lingering questions, I think the overwhelming is that it will, and so I'm going to vote yes.

CHAIR KARRON: Thank you. Dr. Hewlett.

DR. HEWLETT: I'm very reassured by the ability to compare -- or my interpretation that we can make at least a general comparison with the absolute values from the previous trials, and the demonstration of ongoing efficacy in Canada, so I vote yes.

CHAIR KARRON: Thank you. Dr. McInnes.

DR. McINNES: Embracing the comments of my two previous colleagues, I vote yes.

CHAIR KARRON: Thank you. Dr. Royal.

DR. ROYAL: I also so vote yes.

CHAIR KARRON: Dr. Stapleton.

DR. STAPLETON: I concur. Yes, on all three.

CHAIR KARRON: Okay. Ms. Province.

MS. PROVINCE: I vote yes on all three questions.

CHAIR KARRON: Okay. Dr. Gellin.

DR. GELLIN: Yes on all three.

CHAIR KARRON: Dr. Jackson.

DR. JACKSON: Well, I think the data in aggregate do indicate that there is a diminished response to the Pertactin component in Pentacel compared with separately administered vaccines, so the question is, to what degree is that important? And I think the Canadian experience is relevant to that, so while that's a bit of an unknown, I think that given the risk benefit ratio of the vaccine overall, that the data are sufficient to support efficacy against the components mentioned in question two.

CHAIR KARRON: Thank you. Dr. Word.

DR. WORD: I think I'd have to concur with my other colleagues and say yes.

CHAIR KARRON: Okay. Dr. Self.

DR. SELF: I guess I'm agonizing. It feels like more than my colleagues here. For A, I think the answer clearly is yes. For the pertussis component, I -- as a statistician, I guess I maybe put a little more faith in modeling, and even though I would have liked to have seen more detail of the model, and certainly would have liked to have seen that model validated against the Swedish-II data. I mean, it's stunning that that wasn't done. It does seem that the profile would support efficacy, so I would say yes for that.

For the HIB piece, is what I struggle the most about, because it is clear that there were two carefully controlled randomized comparisons, and you got different answers. And I don't know what to believe. Is non-equivalence, is the answer to non-inferiority a yes or no? There's something else going on. There's more variability, and if you ask the question for a given individual, if you vaccinate with ActHIB, or if you vaccinate with Pentacel, I don't know whether they would get roughly comparable antibody titers, and whether the protection would be the same, so I guess for that component, I don't feel like I have adequate data to say yes, I know that

protection for that piece is the same, so I select out 2-B and say no.

CHAIR KARRON: Okay. Dr. Wharton.

DR. WHARTON: I would like to echo Dr. Self's comment. I'm very comfortable with the diphtheria, tetanus, and polio components of the vaccine, and pertussis is difficult every time it comes up, the interpretation of immunogenicity information and trying to figure out what it means is always a problem. I guess in the general scheme of things, I'm pretty reassured about the expected efficacy of the pertussis component of the vaccine, but I, too, have remaining concerns about HIB and the discordant results in the two clinical trials that were presented. And I actually found it quite troubling reviewing the materials that we're 15 years into the HIB conjugate vaccine era, and we're presented information where post dose three GMCs are all over the place, and we have no idea what that means. And in particular, for a vaccine where we have nominally an accepted serologic correlative protection, to then be presented information like this and just not know what to make of it, I find really distressing. So I, too, am not comfortable about the HIB component specifically of this vaccine

based on the information presented.

CHAIR KARRON: Okay. Would you care to comment on what additional data are needed in terms of HIB?

DR. WHARTON: Well, unfortunately, it goes beyond the vaccine whose portfolio we're being asked to consider today. I mean, much of the difficulty has to do with the inconsistent performance of the comparator vaccine, so I think that makes it quite difficult to answer the specific question we're asked.

CHAIR KARRON: Dr. Larussa.

DR. LARUSSA: Well, there must be something in the water on this side of the table, because I pretty much feel the same way, and I'll echo Melinda's comments about the HIB situation. I guess what I'll say is I'm willing to vote yes on these, but I think this is going to have to be sorted out in the follow-up and see what happens with haemophilus disease once this vaccine is used.

CHAIR KARRON: Dr. Larussa, can you just clarify, did you vote yes on all three items?

DR. LARUSSA: Yes, I voted yes on all three.

CHAIR KARRON: Okay. Thank you. Dr.

Butler.

DR. BUTLER: For 2A I vote yes, for 2C I appreciate the conversation earlier. I was struggling with that, but I vote yes. Like others on I guess this side of the aisle, had some concerns about the HIB component. I've also looked at it a little differently, maybe from Melinda. I've also looked at it in terms of what if -- how would we interpret these data if we didn't have a correlate of protection, since for pertussis, for instance, that's how we're approaching the problem. It's without that kind of data. I've had, of course, concern about populations at highest risk, whether or not the immunogenicity data are adequate to suggest protection, particularly after one or two doses of vaccine in very young children, which it sounds like we really don't have data on that. I find the effectiveness data, or the epidemiologic data, which I'm interpreting as effectiveness data from Canada very reassuring. The advantage of starting on this side, I do have the data I didn't have earlier now, thank you, BlackBerry. And even though I'm still concerned that rates in Native children or Aboriginal children in northern Canada may be slightly higher than Alaska, they're clearly nowhere near the

magnitude of the rates of disease we saw in Alaska during 1996-1997, when we were using the HBOC vaccine. So having said all that, maybe it's a little more clearer where I'm coming down, is I vote yes on 2B, also.

CHAIR KARRON: Thank you. And Dr. Farley.

DR. FARLEY: Well, I share the concerns that have been raised about HIB, in particular. I think that the pertussis, given the fact that we have a multi-component approach, that lends reassurance in that regard. But I am concerned about HIB, and I thought we were being asked sort of the over-reaching one question of do we support the efficacy rather than individual here. And I think my vote would be yes, overall, with this heightened level of concern that might lend itself to, in terms of some of the materials that are included with this vaccine, that there would be the question raised, or the concern raised about particularly high-risk populations, and that this might not be considered the optimal vaccine for those who have high rates of disease in the under one year of age group, and that sort of thing. But I do think that deserves some attention, and considering how this will be, the public information

is produced on this vaccine, so I will overall vote yes, having some concerns about HIB, and wanting to have some additional instruction included.

CHAIR KARRON: Okay. As for me, I will vote yes on all three. I think that my concerns about pertussis have been answered. I think I share many of the other participants' concerns about HIB. I think that Dr. Farley's comment is a good one, in terms of labeling and public information. And I also think that brings us into the last question. It's probably a good segue into the last area for comment, which is the issue of post licensure studies, and I was wondering if we want to have comments on that. Speaking personally, I think, obviously, HIB surveillance is a very important component of this. Other comments? Dr. Farley.

DR. FARLEY: I fully agree, and I think we need to point out that HIB surveillance is not just age flu surveillance, and that we really have to come up with a way where we are getting accurate serotyping data, whether it's strictly through the ABCs. Is that truly reflective of the nation? And if not, we need to be serotyping more regularly to make sure we know it's truly HIB disease, and not one of the other serotypes, or non-typable disease.

The other thing that I feel would be very useful is launching some sort of a carriage study as this vaccine is introduced to get a sense of whether we are changing that herd immunity benefit. Are we giving anything up with this? And then my final thought is that while we seem to have a little higher level of comfort about the pertussis aspect of this vaccine, it is a very difficult disease to diagnose in this country, and I'd urge whoever involved in those -- in encouraging better diagnostics for pertussis, so that we can actually monitor the impact with better pertussis surveillance.

CHAIR KARRON: Thank you. Dr. Jackson.

DR. JACKSON: Yes. Echoing Monica's comment, regarding the pertussis surveillance, I think given the fact that even initiation of testing for possible pertussis is initiated on a rather haphazard or lack of a systematic way, and the varying tests with varying degrees of sensitivity and specificity are typically used, that perhaps that issue should be specifically addressed in the post licensure plans to ensure that we have a reasonable chance of detecting a true increased risk of pertussis should it occur in the population receiving the newly licensed vaccine.

CHAIR KARRON: Dr. Modlin.

DR. MODLIN: Well, actually, Dr. Farley made the comments that I was going to, the major one, anyway, which was, if there is going to be some follow-up surveillance, obviously, the biggest bang for the buck is going to do it in those populations that are at highest risk. And it's a little bit easier, it would also be easier to do so with a surveillance set for carriage, as opposed to just for disease, which would be -- I think we all agree would be an adequate surrogate for vaccine effectiveness.

I just want to point out that I think we are wringing our hands basically over one study, the comparator study that showed a lower GMC of antibody, but still the GMC that was achieved in that study at the lower end was at a level that I found relatively reassuring based on historic data, so I guess for that one reason, I'm a little less concerned about the HIB issue than perhaps some of my colleagues are.

CHAIR KARRON: Dr. McInnes.

DR. McINNES: I have one comment about that post third dose scenario, which we know from the HIB study, this is where you see the most variability. The HIB response is very age-dependent. And in fact, a month, a month and a half can make a

difference in a child's antibody titer. And we know that from an extensive set of studies that have been done. I mean, the response is polyclonal, in fact, it may even be monoclonal to haemophilus, to PRP. So I think this is the area where you tend to see the greatest variation post third dose, and then by fourth dose they all look pretty much the same, so I think that is probably where you see this.

CHAIR KARRON: Other comments? Okay. If not, I thank you all, and we will -- yes, Dr. Baylor.

DR. BAYLOR: I wanted to push the committee a little bit further, especially those who on this side who expressed concerns about the response to the HIB, in particular, in the high-risk. Would you go so far as to say -- I mean, there's been discussion about follow-up surveillance, but are your concerns at a level that you would not use this product in that population? I just want to be clear on that.

DR. SELF: I guess I'll start. I didn't actually realize when I answered the question that I had to answer the overall question. I was going one at a time. And I guess my answer to the overall question is yes. I mean, I think this is a vaccine that on balance will have public health benefit, and

should be used. So my concerns, particularly about HIB, I think, are -- well, it's not the veto vote out of the three components, so it should be clear about that.

In terms of the other studies that should be done, I guess I would like to see more work on the serologies, and trying to relate those as best as possible to risk for HIB and pertussis. I can't tell you what study designs in any more detail, what's feasible and what could be done, but it just seems to me that that is an area that really should be explored, both for this vaccine, and then per the comments by Dr. Larussa for other vaccines that are multiple component vaccines that are just going to be coming up. We've got to understand better the joint effects of these things, and we might as well start with this.

CHAIR KARRON: Dr. Butler, do you want to comment on high-risk populations?

DR. BUTLER: Well, it's a very pertinent question. Alaska is a universal vaccine state, and we have the statewide program, which includes the high risk population. And I've actually had this conversation already with both the state and tribal consortium immunization directors. And at this point

in time, if Pentacel is licensed, we will not be changing our current vaccine schedule to incorporate it.

CHAIR KARRON: Yes. Dr. Hewlett.

DR. HEWLETT: I do want to add one more point about the Pertactin issue. While I do agree with what Mike Decker said about in the grand scheme of things it doesn't matter. I agree with what Dr. Larussa said, that, in fact, as more components are added, this is a special set of circumstances. In my mind, there's not enough not to approve this vaccine, but it is an issue, and it's recurrent enough, it seems to me, that it should raise a question. And as things go forward, it seems to me it would be reasonable to follow-up at least to see -- I think the one thing that affected me is the -- if I interpreted correctly, the immunologic data from Canada, where depending on the efficacy data, the vaccine works. We didn't see -- is that correct, Scott -- there was not the reduction in -- if you make those same comparisons, the Pertactin immunogenicity was not reduced as it appears to be for the study in the United States. So I think that, in and of itself, is saying that that needs to be, at least, followed up.

PARTICIPANT: Pre-licensure studies in Canada were substantially smaller.

DR. FINN: You're correct. I think it was my slide that you're referring to. There was some data from 5A9908, which was a pretty large study. It was 1,500 kids or so conducted in the U.S., and in that study, the response to all the antigens appeared to be higher than the responses seen in the U.S. studies, in general.

CHAIR KARRON: Dr. Hetherington.

DR. HETHERINGTON: There's another risk we haven't considered here, and that's the risk of not getting immunized. The sponsor had a nice slide showing that the rate of coverage is increased by using a combination product. And if that's the case, then your overall protection for any population might actually be increased, despite a small and really not well quantified reduction in immunogenicity. So it's something to keep in mind, the high risk here is not the high risk getting the disease by itself, it's also the high risk of not being immunized. And if I recall the overall rates in that slide, they were depressingly low in terms of just people getting all the vaccines that they need to, so I think there's -- in the post marketing world, there might be some

attention paid to quantifying how much improvement in overall vaccine coverage you get with this kind of a product, because it could be substantial.

CHAIR KARRON: Dr. Butler.

DR. BUTLER: Just to comment on that, I think that's a point well taken. I think in certain situations, such as what we have in Alaska, the point becomes a little bit moot because we're already using a combination vaccine for HIB immunization, and there's really, I think, only one visit where we'd be reducing the number of injections, maybe two, so the reduction in injections may be small. I may be focusing a bit much on the first six months of life, but with the lack of any immunogenicity data, and the fortunately limited epidemiological data because of the relatively small number of cases we have both in our high risk populations in Alaska and in Canada, I'm left pretty much to compare the PRPT with HBOC in head-to-head immunogenicity studies in Alaska Native populations that were performed about 15 years ago, and they look very comparable.

CHAIR KARRON: John.

DR. MODLIN: Just very, very quickly. I recognize we've been -- the committee has met to pretty much confine our purview to safety and

efficacy, but Dr. Hetherington's comments, I think, are important. In the State of New Hampshire, we've been trying very hard to get all of the hospitals to institute a birth dose of Hepatitis B vaccine, and it's been difficult to do so because of a relative inflexibility on the part of practitioners with respect to combination vaccines, and introducing this vaccine will clearly help in that regard, as Dr. Greenberg hinted at it during his presentation, so this would be an additional public health benefit, in addition to perhaps enhancing overall immunization rates by a few points, which is no small contribution.

CHAIR KARRON: Okay. I thank all of you for your comments. We will adjourn for lunch, and we will reconvene, Christine, at 2:15. Thank you.

(Whereupon, the proceedings went off the record at 1:13:36 p.m., and went back on the record at 2:27:13 p.m.)

CHAIR KARRON: I think we'll go ahead and get started with the afternoon session, which is an overview of the Office of Vaccines research and review. Before we do get started, it was pointed out to me that we have some members who've been involved in VRBPAC and on teleconferences, but actually

haven't been at a face-to-face meeting before, so before we get started, just so everybody knows everyone else, I wanted to introduce John Modlin, sitting down at the corner over there, and Jack Stapleton, who's right here, and Lisa Jackson, who's right over there. And I also did very much want to thank Erik Hewlett and Jay Butler for being here with us today and participating also as guests. Dr. Self, did you have something to say?

DR. SELF: No.

CHAIR KARRON: Okay. You're not new.

(Laughter.)

CHAIR KARRON: Okay. We're going to start with an overview of the CBER Research program, and Dr. Carbone is going to lead us through that.

DR. CARBONE: Good morning. Okay. Thank you very much for coming. We're a few minutes late, so let me get right to it. I just want to start very quickly with the vision for CBER. Today my goal is to sort of give you the CBER introduction to the research program and research management, and then we'll follow with talks from OVRR, give you a little more detail.

Dr. Goodman, when he came, developed this new vision for CBER, and the important thing that I

want to point out here is the fact that no longer is this viewed as a passive organization that simply receives what it gets, and takes care of it, but actually, the goal of the organization, because of the importance of the products and the public health, as well as for the individual, that need to facilitate these products to usage is quite critical. In addition, because it's now a global community, we want to make sure that the organization functions in a global fashion, wherever possible.

This is just a brief organization chart. Today there are four offices within which research is conducted as part of the office, the product office. Today the office under discussion is the Office of Vaccines, which will complete today the review of the three laboratory-based offices which do research, as well as regulation.

Just wanted to make a comment about the concept of the critical path. I'm sure most of you are familiar with this concept at this point. NIH envisions translational medicine as sort of from the bench to Phase I clinical trials, but our interest, of course, is getting safe, effective, and high quality products all the way through the system to use. Because so much of what happens early in

prototype design, discovery, and preclinical testing affects what happens here in clinical development, obviously, our concern really stems from the beginning all the way to final approval of the product, and clearly beyond in safety and surveillance issues.

Research - in this article that was published a few years ago through the Office of the Commissioner, Research was given not simply a sidebar where so many people have put research in a regulatory organization, which is supposed to be science-led and science-based, but actually have integrated research into part of the regulatory process to help resolve problems that are identified, and challenges, be it an academia, government, industry, FDA, or collaborative associations of those, to actually provide solutions that then can be fed back into the regulatory process.

CBER leadership and CBER scientists, what is their role in this product development pathway, or helping facilitate products making it through to approval. And I wanted to sort of give you our impression of that. We view this as really a triumvirate. There are the - in the work that you will reviewing today, which is what happens in the

intramural research programs within CBER, as well as what has been reviewed, which is our collaborations, working with the intramural program and with external partners. And it is hoped at some point that CBER and the FDA will be able to have a broader influence in the important kind of research that helps answer the scientific challenges that makes it difficult to know how to answer the concerns we have with products, some of which were expressed, for example, in the morning session. And that would be by actually helping external community, facilitating their ability to answer these questions, as well.

The key part of this effort within CBER, though, is the fact that as government scientists and scientists who are interested in classes of products, not simply focusing on a single product, but on entire classes of products, and what we can do to facilitate them through science, it is very important that the work be communicated in the public domain, and that is something we can do.

I want to also point out for your edification - I don't know how many of you are involved in other areas of the FDA, but within the FDA, we have a fairly unique model for researchers, and that is that the researchers are fully integrated

into the regulatory process. They are reviewers, and, in fact, we don't use the word researchers, we call them research regulators. This includes the entire gamut, as part of a team, because we all work in teams, and they're regulatory scientists involved, clinical reviewers, statisticians, research regulators are the only ones that do review, but they are an integral part of the research regulatory team. And they do everything, basically, that the product specialist does, including inspections, which I have personally done myself.

Applicability of research programs - so when you talk about research in the FDA, the first question I got asked is oh, you do research at the FDA? And the second question is, oh, why do you do research at the FDA? And then it seems to say well, okay, I get it, I get it. NIH does the basic work, and you do the applied work. Well, I've tried to actually make it a little clearer, that that's not really what we do. Whatever the science is, be it biochemistry, all the way through clinical trial design, the work, the research work here, the novel of information produced needs to be applicable to the regulatory process, and that's the key, to find out where the issues are, and to do the research to

resolve those issues.

Because our researchers sit on applications, IND, BLA applications, they have the opportunity to identify critical problems, particularly critical problems that seem to be overwhelming in many different types of applications that need to be resolved. And because of both the public health issues with countermeasures for bio terrorism, bio warfare, as well as issues like emerging infection, such as pandemic flu, we have a great deal of research activity in those areas. But it's also a byproduct of the fact that since research resources are somewhat limited in this environment, the funding available in these areas tends to make those areas of higher activity at the center. They're still quite relevant, but the relative proportion of those activities is fairly high.

So types of research at CBER really can be, in my mind, in very two simple ways defined. They either create regulatory pathways where there are none, and if you think of stem cells, for example, gene therapies, these are not standard pathways that have been utilized repeatedly over time, and often need full development. The second one is, and this is important for vaccines,

particularly vaccines that have been around for a long time, like the vaccines discussed today, is that the need to apply 21st century science to improve the current regulatory pathways, more predictive, higher quality input into what we need to be doing. And these I just mention are some areas that through the Office of the Commissioner, have been of particular interest, and molecular medicine and personalized medicine, the concept that identifying where the individual intersects with the product is very important. As you know, in vaccines, minute numbers of proportionate adverse events can cause significant problems and concerns with vaccines. If we took a look from the different direction of how to identify those small number of individuals who are going to have problems with a vaccine, we can tailor the medication better, and use the medication that's good for the vast majority of the people.

Biomarkers are an interesting thing I bring up, because, obviously, having a predictive clinical marker, we were discussing this morning, for efficacy and safety issues, is key. But one thing we've tried to add into the mix with the Office of the Commissioner is for our products, we have biomarkers for the products. Our products are often

living beings, complicated molecules, and we need some type of markers for consistency and quality. How do you test a stem cell to know that that stem cell is going to be a cardiac cell that goes to the heart and causes electrical discharges there, or is that cardiac cell going to go to the brain and cause seizures? Or worse yet, is it going to become a tumor? So how do we predict these things? So, for us, biomarkers of the products hold also an important element.

And novel technologies, as mentioned before, are quite critical, the move from the blots and the gels, and the visual inspection of cells to something which is highly predictive and quantitative and high throughput in terms of predicting quality, again, often of products we're talking here.

As a result of needs that have been identified for the center for years, the majority of our research program focuses on safety, but we also have issues of product characterization, because we do have difficulty characterizing products, and efficacy questions come, such as those that were talked about this morning.

CBER Research - I don't have time to go into great details, but I can tell you that the

research is productive. We have hundreds of publications, guidances, policy documents that are based on research work done here, and collaborative work done with CBER researchers, and outside. It is also research that is leveraged, because, obviously, in any intramural program which is required to cover the breadth that our program is, and the funding that we have, it is imperative that we seek outside experts, and we have, at this point, at least over a hundred collaborations with outside scientists, eventually formalized this process into something called the CBER Collaborative Scientist Training Program, and we now - we've opened a web page where those sorts of collaborations are listed, and we're trying to form bridges with institutions so that the institutions are aware of the interesting elements of the science devoted to product quality and clinical regulation issues that we deal with, so that we have the opportunity to train outside scientists in this specialized type of research.

So what are we doing within CBER Research in the last four years or so under Dr. Goodman's leadership? We have developed a research management process which involves the research leadership council. And I want to make very clear that our

research management is not done purely by research regulatory staff, like myself. The research management council is composed of center leadership, and the research regulator, and the regulatory scientist. All of the priority setting we've done, the research management activities we've done, which I will highlight, all done in a committee organized and composed of cross center types of staff. Because as one of our scientists said, if it isn't clearly important to regulatory scientists at CBER, it shouldn't be done.

So one of the things that this has done, in particular, in one of the areas that I think is important, my role is quite important, is to make sure that the inter-office communications within the center occur at high levels, and at every level. But, in addition, it's important across the FDA to foster inter-center, as well as external communications with the outside. We, for example, are hosting an academic institution coming to talk to us about opportunities for collaborative research, and we've identified that there are issues in the CDRH, which is the Center for Devices, so they will be brought into the mix. So we're trying to work across the center, as well as across the FDA, in our

research.

Our goals also are to make the kinds of prioritization and goal setting we do better, but also to make it transparent. We want to develop consistent and valuable outcomes evaluation processes, and as you know, we're probably one of the centers that use the most extensive external scientific, and expertise evaluations in the center for individual laboratory programs. This effort to take these offices raised that to a level where the entire Office of Research Programs thinks site visit -- and one of the things that I've recently instituted is, this year, starting `07, and for every office site visit that's been conducted, a formal response back to the Advisory Committee on their report, so the committee will be sending us reports on individual laboratories in each of the offices, and there will be a formal response by the laboratory site visited, and/or the office site visited back to the committee as to how they're going to the suggestions and advice of the committee, and work on those. And, of course, this group is tasked with ensuring that broad external and internal input continues in our programs, because we all know science is a global community.

The guiding principles are fairly obvious. We're in the process of putting them up on the web site now, but it's important to state them, and state them explicitly. They're in your book, and I'm probably already running over, so I won't go through them, but they're common sense, and they're important to us, and it's important to keep these in mind. Whatever we do, actually perform the research, as well as manage research. So there isn't time, of course, to go through specific paradigms of how we do priority setting across the center. However, I just want to sort of give you some insight into the kinds of thought processes that we go, and the kinds of criteria that are important to us.

In terms of deciding what to work on and when, one of the most important things is the directness of the regulatory impact. If this is a licensed product, if this product is out there being administered to people, and an issue arises, the scientific challenges must be addressed, because there is potential for harm. There is also potential for what could happen, the efficacy is limited. If the issue that we identify from the regulatory and other processes is a critical bottleneck, we could do this if only we knew that, that becomes a high

priority. Anything that's far-reaching, that goes across a whole product category, and we have the fortunate opportunity to see what happens with products of multiple sponsors, and if we see a problem that is coming recurrently, the problem is a bottleneck, that becomes a high priority issue.

We have to take into account, though, not just what sounds good, but what we can actually make some achievements on. And as you know, with our resources being limited, and about 70 percent of our supply consumable type funding, post doc funding coming from other sources, collaborative work, we need to be very careful that if we commit to something, we can actually achieve it. So the probability of success with current or achievable resources through collaboration is critical for our consideration. In terms of getting something done, we need to know that the scientist proposing can do the work, and this is where in particular the expert outside site visits we have on each scientist are very important for us. So we need to know that the return on the investment is going to be there. We don't have the opportunity to work in the theoretical realm.

Rapidly emerging public health crises

need to be addressed, and if they involve a biological product, we need to address them. And, in addition, we need to think about the future, such as pandemic and preparing. We can't - you know the titanic of research is not always the swift response, it's not always there, we need to think ahead. There are several cases, many of which I can't tell you because they're proprietary. We have used scientific expertise in the center to resolve a problem quickly, and some of them I can, and you'll hear about those today. Some we can tell you because these are published, these are available for every sponsor, every interested party to use, and they will be elucidated today.

And then we also take into account what we can do uniquely. There is a huge research community out there, but we know that our scientists are one of the few scientists working in a public domain that have both product expertise and scientific expertise, so that taking that unique expertise and applying it in ways that other people don't think of applying it, or there isn't available funding, or the project is fundable in a standard extramural system, is something that we find goes high up on our list. And, also, because of this

expertise, if we hook up with people with standard scientific expertise, we can often do things that wouldn't have been done, otherwise. And, finally, whatever we do must be of high quality, and this is in part why your help and advice in this site visit is to important for us, and we appreciate your time for this.

So to put that in sort of a flow diagram of what the process, we developed the research leadership council. Again, I'm sorry I don't have time to give you the details, is basically the concept goes, we start with what it is we do, both from a regulatory point of view, what is coming into us, which interestingly to note, it's not something we control, but we have to address, but, in addition, we take the bigger picture and note what is a public health issue.

We identify the unmet scientific needs. What are the scientific challenges to banding those products through quickly, they're safe and effective. And once we identify those, we develop the priority list based on those.

The office is tasked with developing a yearly scientific plan and budget, which is also at the end of the year evaluated as to its success. And

then we hope the Advisory Committee could play a key role in reviewing both the plans that we propose, as well as the outcomes that have been achieved on a yearly basis, as we then go through the cycle once again and use this information to change what we do, have proposed to do in our plan. So this isn't currently being instituted this year, next year we will fully implement it, because as you know, any new process takes a while. And by the third year, it will be fully in place. And you'll be hearing more updates about this.

So this basically says the same thing in words, and it's in your document, so I won't go and say it. And I'll just thank you very much. It's Thursday afternoon, it's late. Unfortunately, there's flurries out there, but I don't think there's accumulation. So we greatly appreciate the fact that you're all here, and we greatly appreciate hearing your advice. I'll take any questions.

CHAIR KARRON: Thank you. Questions for Dr. Carbone? Okay. Oh, I'm sorry. Dr. Hewlett.

DR. HEWLETT: On your next to the last slide, your flow diagram, the second box, "Unmet Scientific Needs", I wondered what the process is by which you go about identifying those. The experience

we have is oftentimes if you just have somebody list what the problems are, there's a standard list of problems, but if you get a bunch of unbiased people with different perspectives in the room, you can identify things that seem, that are routine and are obvious to you, but are not even seen by the person that's doing them all the time.

DR. CARBONE: I think that's an excellent question. I think there's really two-fold answer to that. The first thing is, we have a scientific charge that comes in the door, and that is, suddenly we see a huge rise in boo-boo vaccines, pre IND meetings coming down the pike, and we realize suddenly that there is no way to predict whether the boo-boo vaccine is sufficiently attenuated. And so by the sheer volume and importance of the workload, and the gaps that it addresses, first Rotavirus vaccine caused a series of problems, which we had to react - I shouldn't say problems, series of issues that we had to react to, so that's one. The second one is obviously the regulatory, I'm sorry, the public health portfolio, scanning just like CDC and any other organization to prepare ourselves for crises. And, of course, things that are threats of crises, we hope to have time to prepare, such as

pandemic flu. Sometimes we don't, such as West Nile, and given the limited resources, we must take those kind of crises and urgent things first. We would hope at some point to have the luxury of enough funding to be able to be both a long-range planning and a crisis reactive, so that's obvious.

Then the second step, and this is something I will say quite frankly is in the works, and that is taking these sort of qualitative - so we have our list. We take our list, now we apply these qualitative issues; what can we do? What are we capable of, what is everybody else not doing? That has to have a structure to it. And, as you state quite clearly, has to have some external validation or comment, so the plan at this point is to take these kinds of qualitative criteria that would move something up or down, and develop a formal process where this happens. I can tell you that hasn't - that formal process is in the works, and you will be hearing about it when it is formed. And I think that no matter what we develop, no matter what we think is important, the key at the very end is going to be the purple box, to make sure that we can get the external comment from the stakeholders, from the experts like yourselves, to give ourselves reality checks, so it's

really a three-fold. The work load coming in in the public health issues, what we can do, sort of the qualitative issues that I was saying on that slide, and then, finally, the modification from the external group. It is in process, and by next year I should be able to give you more specifics on that.

DR. McINNES: Kathy, in the scenario that you lay out, it just occurred to me, do you have I'm not sure hiring authority is the issue, but when you need to bring in a particular technology or technique, or approach quickly, and you don't -- how do you go about doing that? Can you bring in expertise under IPAs and things like that? Is that how you do it, or you wait to grow it, because by the time you hire people, you know.

DR. CARBONE: It's really a combination. Quite clearly, we tap into the external community, there's no question. There is a conflict issue, and we have to deal with it, but we go to the experts. In fact, we are very good at convening - I think West Nile is a good example of that - pulling the basic researchers out there with experience in West Nile, in the blood industry, the device industry, as well as growing our own experts who developed a knowledge base internally; which, as you point out, takes a

long time. So this is why, in a sense, the critical part, component of this is the predictability. What we can predict long range, and we have to prepare for. Resources are extraordinarily tight, and any kind of new hiring is very difficult.

I have to compliment the center and the offices, for example, in some arenas, they've been able to reformat and realign resources, and actually not in one office, but by combining resources across offices, develop or start to develop an expertise which we didn't formerly have, which we feel is important long term. So we definitely use the outside sources, absolutely, but sometimes we need to grow the inside, and that becomes - it has to be prioritized. We can't afford to do everything we need to do.

DR. GELLIN: Kathy, given that your peer regulatory agencies around the world are probably grappling with similar issues, what's your ability to work with them on some of these issues, and the degree to which to make a decision to divide and conquer. You guys work on this one, we'll work on that one, and compare notes.

DR. CARBONE: We actually work with them quite extensively, and have a lot of collaborations.

And we're actually a WHO, remind me on the verbiage, a WHO collaborating center officially, and that's with the NIBSC in the UK. For example, there are many things we simply can't answer on a single agency platform. We have in the TB arena, in the mumps arena, cooperative evaluations underway for standards, for assay validation with international organizations across the world. So we do, indeed, divide and conquer, and every group has its strengths. You're actually right. Canada has used us extensively, for example, for helping them with reviews of their program, and collaborations with some of their programs in the MMR arena, and proteomics arena, so we do, indeed, try and leverage amongst all the various agencies. In fact, we have to for many of these issues that are global.

CHAIR KARRON: Okay. Thank you, Dr. Carbone. Dr. Baylor is next.

DR. BAYLOR: Good afternoon. My task is to give you sort of an overview of the FDA's Office of Vaccines Research and Review. Our mission statement is in sync with the mission statement of the FDA, as well as CBER. And, basically, that's to protect and enhance the public health by assuring that products are available, and that those products

are safe and effective, and the products we regulate in the Office of Vaccines, vaccines and other related products.

How do we accomplish this mission? We accomplish this mission by reviewing, evaluating, and taking appropriate actions on a variety of submissions, such as investigation of new drugs, biologics applications, amendments, supplements. We plan and conduct research related to the development, manufacture and testing of vaccines and related products. We're also involved in developing policy and procedures governing the PM market review, and evaluation of the products we regulate. We are also involved in evaluating and testing licensed vaccines and regulated products. We also evaluate and monitor clinical experience and reports of adverse events, as necessary, and coordination and cooperation with CBER's Office of Biostatistics and Epidemiology. We also, as Kathy had indicated, participate in inspections of manufacturing facilities, and we also participate in national and international outreach activities. As your question, Bruce, we have quite a number of international outreach activities in the Office of Vaccines.

This is the organizational chart in OVRR.

Basically, we have four divisions, Bacterial Products, Viral Products, and we have an applications division that handles the incoming applications. And we created since the site visit, we formally created a new division, the Division of Product Quality, and that was not part of your evaluation in the site visit.

The role of research in the Office of Vaccines, basically, it supports the science-based regulatory review and decision making. I mean, that's foremost. It provides the expert talent we need to review regulatory submissions, as those I've mentioned. It also allows us to address product-related issues in the laboratory, as the need arises. And it also influences our policy and guidance on new technology, such as the recently published guidance on cell substrates.

We believe that research is an essential component in CBER and the Office of Vaccines. It's essential to the regulatory review process, to make sure the products are safe, pure and potent, and effective, and the research needs to be sufficiently open-ended so we can have the ability to respond to new areas, as they arise. And, lastly, the research serves as a tool to recruit and maintain highly

qualified scientists.

As far as priorities of the research, within the broad range of the various scientific disciplines, we have to have certain programs maintained, the regulatory review process really drives our research priorities. It's critical that we have broad research expertise in the vaccine and related disciplines, such as bacteriology, immunology, virology, what have you. And this allow us to shift our priorities when public health emergencies arise.

Our research projects and their relative priority, of course, these change over time, but this is necessary to continually evaluate our research needs. As far as the process of setting priorities, the ultimate decision on prioritization results from - it's subjective, but it's reasoned. The priority setting is based on relevance, such as the nature of the research program, depending on the importance and outcome of the implications for an extensive set of issues, such as product safety, or product characterization, priority setting by uniqueness and feasibility, is there special considerations that compel the project to be done by our scientists, as compared to other scientists maybe at the NIH or CDC.

It may be a special niche that our scientists are the most appropriate to conduct these projects, such as potency assays, and seriological assays. And then there are special considerations, such as the research programs must be able to rapidly respond to emergencies as they arise. The high priority research areas in the office, safety, product characterization, identification of immunological mechanisms, mechanisms of pathogens, pathogenicity, as well as emerging issues.

How do we evaluate the research programs? These are performed on at least an annual basis in the office. The process begins in the divisions. The evaluation is of the principal investigator's research program by the lab chief, or division director. The progress of the investigators are evaluated. We look at publications, their presentations, what type of outreach they've been involved in, and most importantly, their regulatory workload. And not just numbers, but also the quality of the reviews that they've done, and the interactions and information they provided to sponsors.

We also have evaluations of the Division of Research programs to address the regulatory needs

of the agency, the emerging issues, future issues, and recommendations made by external advisory groups, such as yourself. The individual principal investigators are also evaluated for promotions by the CBER PCE Committee.

Sources of funding for the Office of Vaccine - the basis of our funding is from appropriations, but we also have funding through extramural sources, or I should say external sources. And this, the National Vaccine Program Office, every year we receive some percentage of those funds, the Bio Defense-related awards, we have inter-agency agreements with the NIH, CDC. As I mentioned, the cell substrate inter-agency agreement with the National Institutes of Allergy and Infectious Disease, and also, the Vaccine Development Partnership with NAID. And we also have CRADAs from the universities, foundation. One example is the AERAS Foundation for the TB assay.

The outreach activities, we have a number of outreach activities. And I'm not going to read all of these, but there are several with sister agencies, there are meetings with academics, other international activities, such as the WHO and the PAHO biotech engagement programs, and we also have a

CBER global vaccine initiative, which is very important part of our projects.

So, in summary, our research programs serve to recruit, retain, and maintain highly qualified scientists who have the necessary knowledge and technical skills to conduct research and review that will facilitate the development of new and innovative vaccines and related products that are safe, effective, and contribute to the health and well-being of the nation. That's it. I'll take some questions, if you have them. If not, Dr. Brennan, our Associate Director for Research in the Office of Vaccine, will speak next.

DR. BRENNAN: Well, thanks everybody. First, I want to thank the subcommittee that reviewed us back in May, and there was a lot of hard work. We have the largest research program in CBER, a variety of different research, both in bacteriology and virology. I know Dr. Royal is here, who was the Chair, and Drs. Karron, and McInnes, and Hewlett, and Word were all on our committee, so thank you very much. It's a big effort, and we appreciate it.

Also, I want to publicly thank the scientists, those of you who have been on these site visit committees, appreciate how much hard work it

is, both on the regulatory workload, and the research side, and they get very little recognition, so I wanted to take the opportunity to publicly thank them.

And so I'm just going to show just three or four slides, and since Dr. Carbone has outlined the research program for CBER, and Dr. Baylor has outlined the mission of the Office of Vaccines, I wanted to focus my attention on the area that had the most discussion at our site visit, were those questions about how do we actually choose which research programs that we support, and how do we improve upon them, how do we make these decisions about which new programs we should start, and which ones we should continue supporting, so I'm going to focus my attention on that. Following Dr. Walker and Dr. Weir, the Division Directors of Bacteriology and the Virology Divisions, we'll give you some more specific examples of the types of research that we do in their programs.

And so first, some of you may be familiar with what's been called the KORN report. There was a comprehensive review back in 1997 and 1998. The report came out of the research at CBER, and they gave a very nice list in their report of bullets that

indicated why they thought research was important to CBER. And in the Office of Vaccines, we have used these ideas that came from this external report to evaluate and look at our research programs. And you can see, for instance, we recognize that relevant to all of our regulatory decisions, is the need for a cadre of scientists that are answering relevant and interesting scientific questions, and they're also using state-of-the-art tools to do their research. And this is what this first point was getting at. And we have a large number of scientists who are using the most recent tools for genomics, and proteomics. We have an MMR, for instance, where are using now the IVUS technologies to look at the dissemination of infections in animal models, so we are trying to stay on top of that so that we are using the latest technologies.

Secondly, the research offers the ability to assess risks of new vaccines and therapies. And Dr. Carbone's research on neurotoxicity assays, for instance, is a good example here. And we have many other examples where our research programs involve the characterization of new animal models, which can then be used to look at both the safety and immunogenicity questions for new vaccines that we are

regulating.

Thirdly, the ability to provide a timely response to new and emergency issues. We have two good examples here, one is our response a few years ago to the counter-terrorism issues, and we have a number of programs which existed at that time, and this may be in answer to a previous question to Dr. Carbone, where we actually transitioned some of our programs, like Dr. Burn's program in Pertussis, for instance. Part of it has transitioned into anthrax, and we have programs on tularemia and smallpox, and botulism toxin. More recently, another example is our response to the pandemic flu issues, and our expansion of the seasonal flu program into a program that can address pandemic flu issues.

To anticipate future needs, research adds here, I think, a good example here is a number of years ago we supported a new program on DNA vaccines. And, actually, it was some of the original research on nucleic acid based vaccines which uncovered a number of potential issues, safety issues, as well as immune and vaccine delivery issue for DNA vaccines. Research suggests new approaches, and develop assays. I won't go into it. There'll be more examples from Jerry and Dick after me, enhances our ability to

interact with other agencies, problem solving with Pharma is one of the - when issues come up under IND or BLA, mostly CMEC issues, that our scientists have the expertise to help manufacturers problem solve in these areas.

And, lastly, the ability to retain staff. So our science programs allow new blood to come into the office through the hiring of post doctoral fellows. Many of us started as post doctorate fellows, or staff fellows who have stayed on to become permanent members and future leaders in the organization. So that's what we've used, and this is also what -- what we've used traditionally in the Office of Vaccines then to prioritize our research efforts have basically been in three major areas in the past. And we're starting to move into new area, which I'll discuss on the next slide through the new research program that Dr. Carbone discussed. But in the past, we have, basically, formulated our new research programs based on these three principles, to address regulatory issues for approved products, and I think in your earlier discussions today you saw a good example of how our research in the past has contributed to the regulatory process. Jucilla Burns has a research laboratory, Bruce Meade has one of the

methodology laboratories. Actually, Theresa Finn was in my lab many years ago when I had a Pertussis lab, and Karen Farizo actually was in Jucilla Burns laboratory, so there - and they've progressed now into the applications division, so you can see a good example just what happened this morning with all that expertise in Pertussis, and DIPHTHERIA, and Tetanus, et cetera.

Secondly, to anticipate regulatory issues for new products. There's a number of examples here where - I wrote one down and I forget it now, so I'll cheat - global vaccines, how could I forget? So TB and HIV. Another program I wanted to mention, I think Jerry will mention it, is we have a crosscutting program on cell substrates where we're looking at new cell lines for virus vaccines. And our work in the past on the polysaccharide vaccines, which I think Dr. Walker will mention.

Again, our response to public health emergencies - again, here are our response to the counter-terrorism and the flu, is a really good example. And we also recognize that, again, that this helps us maintain our scientific expertise to do both regulatory and research within the Office of Vaccines. And the other comment here is, we try to

always implement recommendations from external reviews, like the one we'll be getting today, and from the site visits of our laboratories.

So the last slide on priorities here, so Dr. Carbone has done a great job over the past year trying to sort of federalize us across CBER. We have a number of offices with research in blood, and the Office of Cell Therapies, and the large one in vaccines, and trying to bring us together, to consolidate us, to have common goals so decisions can be made on common themes for the CBER Research program. And so, using input from the scientists in the Office of Vaccines, right now we have come up with these three major research priorities that we want to focus our research programs on, and they're not surprising in the Office of Vaccines, but we hope that most of our programs can either meet these. If they don't, then we could make decisions about whether they should be retained within the Office of Vaccines. And, also, to see whether there should be new programs. And Jerry and Dick will give a number of examples of where we see the research programs falling under these three major priorities of developing methods and models to assess both vaccines and biologics, safety. These are basically focused

on safety and efficacy. And this is a facilitation priority to facilitate the development and evaluation of vaccines. And, lastly, to improve vaccine quality. So using input from both within house and from external sources, we are now working on these as our three major principles for our research priorities within the Office of Vaccines.

And my last, well, second to last slide here, all of this said, there are many challenges, I think because of the fiscal environment we live in. There are limitations to the way we can expand our new research programs and recruit staff. There are restrictions to promoting outstanding junior scientists into their own innovative projects. Leveraging opportunities for outside funding is important, but we also have to be careful of conflict of interest issues, for example. And, also, we have to keep external programs within our own research priorities, which also is another issue that we have to be aware of.

Communication of our research successes is something we could do better at. One of the ways we do this is by researchers going to meetings to present their research, and to also talk at regulatory workshops. Again, fiscal constraints have

limited us in some areas there, basically due to the last bullet here, which is travel to scientific meetings.

I just wanted to put up the last slide, which is a Gary Larson cartoon. The reason I put this up is that some days when the regulatory work has been tough, and the research experiment hasn't gone right, either on a day or a week, and you get a phone call that says, and why do you do research at CBER? And sometimes you just want to go out and light one up, but then we realize if we do that, that we might go extinct, so we come back fighting every time, and we come to you and we ask for comments on our research program. And keep going ahead no matter what the issue, so thank you very much.

CHAIR KARRON: Thank you, Dr. Brennan. Questions? Okay. I was actually thinking that in the interest of weather, and given that we all came together relatively late, that rather than take a break, we just march on through. I sense a unanimity of opinion, so next I'm going to call upon Dr. Weir to talk to us about the Division of Viral Products.

DR. WEIR: Thank you. I'm Jerry Weir, Director of the Division of Viral Products, and I'll give you a quick overview of our division. And in

the interest of time, I'll try to be fairly brief.

Basically, our mission coincides with the mission of the office and the center. We do essentially two things in the division, regulate viral vaccines, and related biological products to ensure their safety and efficacy for human use. But we also try to facilitate the development, evaluation, and licensure of new viral vaccines that positively impact the public health.

In support of that mission, we have numerous responsibilities. You've seen most of these already in some of the other slides, so I won't spend much time elaborating on them. But our staff does review investigation of new drug, biologics license applications, we review BLA supplements, we've involved in lot release and testing, and other post marketing activities, such as product deviation reports. We participate with other groups at CBER in manufacturer inspections, both pre and post licensure, and we have a fairly extensive role in consultation with other public health agencies, CDC, NIBSC, WHO, for example. And, finally, last but not least, the staff conducts research that's related to the development, manufacturing, evaluation, and testing of viral vaccines.

The next slide shows the licensed viral vaccines that we have. This is actually slightly out of date. We prepared this last May, since then, these are general categories of vaccines that we have licensed, bio vaccines that we have licensed, but since this slide was prepared, we also licensed last year a papilloma virus vaccine. The next slide shows a list of some, but not all, of the viral vaccines that are under development that we deal with on a fairly routine basis.

The point of these two slides is not to quiz you guys to see if you're paying attention, but it's to point out and hammer home the fact that these vaccines are licensed vaccines, and the ones that are far along in development are a major driving force behind the research activities that we pursue at CBER, and in the Division of Viral Products.

The next slide shows a quick snapshot of the division. This was also from last May, and a couple of updates on it, but, basically, the division is divided into seven laboratories. The 17 tenured principal investigators with a staff of about 70 full-time equivalents. To supplement that full-time equivalent staff, we have about 50 contract employees. Most of these are post doctoral fellows

in the different laboratories, most of whom are supported, almost all of them are supported by outside funds that the staff brings in.

In the last couple of years, we had over 140 publications in this group, and I listed in FY 05 more than $3 million in outside grants were brought in by the staff. Actually, that was updated significantly. I think in FY 06 we brought in more than $5 million. And as already mentioned by one, or maybe more of the previous speakers, we subscribe to the researcher reviewer model. We have a extensive review workload of INDs, BLAs, and other type of work, but we conduct mission relevant research. And as I said earlier, we have extensive outreach and collaborative program with other public health agencies.

The research priorities, Dr. Brennan mentioned three basic ones for the office. I've listed these again here, with some sub-bullets under each one, just to show you some quick examples of the things we do, and how they fit into these priorities. For example, the development of methods and models to assess and predict viral vaccine safety and efficacy. We have programs and projects that deal with the development and evaluation of novel

vaccination strategies and technologies, work that's focused on identifying correlates of protection, and the development of animal models that can be predictive of efficacy.

In the efforts to facilitate the development and evaluation of vaccines for high priority diseases, one of the examples I have influenza vaccine reagent preparation. We also have several programs that focus on various issues that are related to vaccine development of these diseases, diseases such as RSB, Hepatitis C, pandemic influenza, HIV, West Nile, Smallpox.

And, finally, evaluation of novel approaches to improve vaccine quality. We have a program, actually, more than one program in the evaluation of the cell substrates that are used for vaccine production, and the development and evaluation of new methods and assays for product characterization.

The division is divided, as I said, into seven laboratories. The names of these are listed here, the Laboratory of Hepatitis viruses, the Laboratory of DNA viruses, Laboratory of Respiratory viral diseases, the Laboratory of Immuno Regulation, Laboratory of Vector-Borne Viral diseases, a

Laboratory of Retroviruses, and a Laboratory of Methods Development. This organization roughly reflects the type of products that we regulate in the division.

And the last slides I'm going to quickly go through one slide for each of these labs. Not give you an exhaustive picture, but to give you representative examples of the type of research that are conducted in these laboratories. And you'll see as they're listed how they fit into those priorities that we listed a minute ago. The Laboratory of Vector-Borne Viral Diseases focuses its research on the characterization of candidate live attenuated Dengue and West Nile virus vaccines. Also, the mechanisms by which Flabe viruses repair attenuating three prime terminal deletions of genome RNA, virion morphogenesis, the effect of quasi species character on phenotype, and also we have an effort in the development of a ELISA-based potency assay rabies vaccines.

The Laboratory of Hepatitis Viruses focuses its efforts mostly on Hepatitis C, vaccine strategies to prevent Hepatitis C infection, the development of mouse models for Hepatitis C infection to replace the chimpanzee, the development of in

vitro culture systems to study antibody neutralization of Hep C, and biomarkers for Hepatitis C protection.

The Laboratory of Immuno Regulation focuses its research on the structure, function, and analysis of HIV envelope glycoproteins, vaccination strategies to enhance vaccine immunogenicity, and dissecting the neutralizing antibody response to vaccinia virus.

The Laboratory of Respiratory Viral Diseases. This has been a very active group in the last year, and we've expanded it somewhat, but the areas of research here are focused primarily, or not exclusively, but primarily on influenza viruses, and research. They prepare and distribute influenza virus reagents to determine purity and strength of influenza vaccines. They perform serology studies in support of influenza strain selection. They develop high-growth influenza virus strains for vaccines, and determine the properties for optimal growth in eggs and tissue culture, as well as evaluate new vaccine strategies. Other parts of the Respiratory Virus lab identify cellular, focused on identifying the cellular receptors for RSV, and the antigenic structure of RSV glycoproteins. And they also work

on developing serological methods for vaccine trial evaluation, particularly Measles.

And the Laboratory of Method Development. Areas of research in this laboratory focus on micro arrays and other molecular methods for the analysis of pathogens. These include the genotyping of viruses and bacteria, the identification of microplasmas, and the genetic stability of live viral vaccines. This lab also focuses on developing immunological test methods, new animal model development, and neurotoxicity assay development.

The Laboratory of Retrovirus Research, as you might guess from the title, focuses a lot of its efforts on the development of assays for HIV, but also Smallpox clinical trial evaluation, the identification and characterization of adjuvants, the activity and safety of DNA vaccines and CPG oliogodeoxynucleotides, safety and evaluation of cell substrates used for vaccine production and retrovirus transmission.

And, finally, the Laboratory of DNA viruses. Areas of research in this laboratory include the evaluation of cell substrates used for vaccine manufacture, developing methods to evaluate the risk posed by the use of neoplastic cells for

production of viral vaccines, detection of adventitious agents, mechanisms of viral latency, immunogenicity and pre-clinical ethicity of new generation Smallpox vaccines, and evaluation of novel herpes virus vaccination strategies.

So, in summary, the research programs, and the laboratory activities in the Division of Viral Products support the regulatory mission of the Office of Vaccines, and these efforts ensure, are designed to ensure the safety and efficacy of regulated viral vaccine products, as well as to facilitate the development and evaluation of new virus vaccine products. I'll stop there.

CHAIR KARRON: Thank you, Dr. Weir. Questions?

DR. GELLIN: I have one.

CHAIR KARRON: Yes, Bruce.

DR. GELLIN: Tell me - the question is about animal models, and how your work on animal models intersects with the work the NIH does, and how it might also interplay with things that CDER does. You know, my world is all around flu, and there's been a lot of discussion about how animal models might help us to address questions not only evaluating products, but also potentially

transmission, as well. So I'm just trying to think of how animal models cuts across all this, and bridges with either other places within FDA, or within HHS.

DR. WEIR: Okay. Well, actually it's important to us for several reasons. I mean, the animal model issue is important for how you evaluate new vaccines, in particular, but for us, there is also the element of some vaccines will have to be licensed by virtue of the animal route, so these are issues that we face, and what we try to do is decide which ones are important for us to contribute to. A lot of this work is done in conjunction with NIH, for example. Just to give you one quick example, in the Smallpox vaccine world, animal models there are important if we were going to license new generation vaccines. We actually have an inter-agency agreement with NIH, and we work extensively with these guys to determine the best use of the animal models, which ones should be developed, and which ones we should put our effort into. So I think it is for a collaborative effort to do this, but again, we try to target the ones that are important for us, which ones we need to know information about in order to make regulatory decisions down the road.

CHAIR KARRON: Dr. Royal.

DR. ROYAL: Moving forward, are you able to say anything about how fixed the names of the various laboratories are? For example, I'm not suggesting that they should be changed, but Smallpox is within the Laboratory of Retroviruses, and you can imagine that over time, opportunities come about, focus changes, and you start getting sort of inter-mixing of a lot of different work and research. And how do you sort of -- I guess as time moves on, one could have a situation where you just have a lot of different research going on in different labs that maybe initially weren't meant to accommodate that research, or those researchers, or could you say something about how Smallpox ended up getting sort of lumped with retrovirus research?

DR. WEIR: Okay. I'm not sure I could hear all of your question, but are you referring to how we would switch priority?

DR. ROYAL: The Smallpox work end up getting placed in the Laboratory of Retroviruses.

UNIDENTIFIED SPEAKER: (Speaking from unmiked location.)

DR. ROYAL: Yes, after a while, externally one sort of - may have a tendency to get a

little confused in trying to sort of figure out what work might be done in a specific laboratory based on the name of the laboratory, not that that's - or is that important after a certain point?

DR. WEIR: For example, when you see something, an example like Smallpox that's in multiple laboratories.

DR. ROYAL: And that specifically it seems in the Laboratory of Retrovirus Research.

DR. WEIR: Okay. Again, I think the reason is because even though the laboratory names don't change over time, they can change, but we usually don't. The issues do drive what is done. For example, several years ago when we had a major effort to increase the studies that we did in support of bio defense vaccines, we actually supplied resources to any number of investigators that were willing to shift the priority of their work toward these things that we felt was not only a division of importance, but also importance to the Office of Vaccines. And so sometimes within an individual lab, as you point out, there will be projects that are not reflective of the nature of the laboratory. That same process is underway now, actually, for influenza. In the last year, obviously, the last two

years since influenza has become such a major priority, we have very talented investigators that have ideas of things that they can contribute, and they propose to start studies. Many times these are funded by outside funds, but sometimes internally, but it's driven by whatever the issue is.

DR. ROYAL: Thank you.

DR. BAYLOR: We understand the question, and Jerry is absolutely right. But I think it also shows the flexibility. Number one, the divisions that we put up, these are not in concrete, so I mean, there are collaborative efforts going on, not just amongst laboratories in one division, but also across the center, across offices. And when assays are developed in one area, and that we can use those assays for other products, we take advantage of that.

Also, we have been looking at, as we evaluate our structure and our organization, we have been looking at well, are there areas that we should modify? Maybe this is not the perfect way to divide up the laboratories any more. This is sort of legacy. This is historical, so maybe there are other - we're looking at other ways that might be possible to do that. But I think the key here is the

flexibility. Although we may seem very large, we're not, and we have limited resources, so when you can take advantage of crosscutting issues, and going across center, across office, across laboratories, we take advantage of that.

DR. WEIR: And, actually, can I add one more thing to what Dr. Baylor just said? This applies also to our review work, too. For example, in the last year when the number of regulatory submissions for influenza has grown so dramatically, we don't restrict the number of people that are involved in the regulatory review of those just to the ones that are in the respiratory viruses. We reach out throughout the division to make sure that there's somebody with the expertise to do the review work, as well.

CHAIR KARRON: Dr. McInnes.

DR. McINNES: A real world experience. I mean, if we hadn't had Hannah Golding and her assay development expertise turn her attention to Smallpox assay development, we would up the creek without a paddle, so you could essentially draw functional groups that work across these, and come together in team, and I think that's what you were getting at.

DR. WEIR: Yes, and that's what I meant -

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DR. McINNES: You've kind of got the structural piece, and then you've got the functional piece.

DR. WEIR: And that's sort of what I meant about trying to take advantage of the existing expertise.

DR. McINNES: Right.

DR. ROYAL: We are seeing the same sort of thing develop in clinical academic departments with pathology departments aligning with surgery, and there are lots of examples of that sort of thing.

CHAIR KARRON: Dr. Larussa.

DR. LARUSSA: Well, what I thought you were going to say was that since most of the HIV vaccines are vectored vaccines, that it made perfect sense to have those people sitting next to each other.

CHAIR KARRON: Yes, Dr. Farley.

DR. FARLEY: I think that the issue of having people doing things that overlap with each other scattered about comes up when you do the individual laboratory reviews, as well. And I think the bio defense area, and probably now hearing that the funding was sort of put out there for people who

are willing to shift and use their expertise for needed new emerging problems over the last five or seven years, kind of explains where these things have kind of come up all over the place. And it's reassuring to hear that they are sharing their expertise horizontally, as well. And maybe there would be room to, not necessarily formalize it, but to make sure that's being widely encouraged, and that there's a lot of interchange between people who are in lots of different, technically different laboratories within CBER, but who are doing things that could easily result in good collaborations.

DR. WEIR: And a lot of that does occur. It occurred in both the example you gave with bio defense several years ago, which not only did we have working groups, but even one laboratory, like the Laboratory of DNA virus, would include members in other laboratories that have related products, so they do get together and do that. Same thing is happening now in influenza, where we've spread out both the workload, as well as the types of research projects.

CHAIR KARRON: Yes, Dr. Larussa.

DR. LARUSSA: Just one other comment, and this is more of a generic comment than specific to

your division. But a number of us who have done reviews of laboratories have been both impressed and worried about the amount of research that's dependent on external funding, and we would want to know whether there have been discussions about addressing that, so that you're not being held hostage to other agencies' agendas.

DR. CARBONE: Well, let me backtrack just a hair about the cross center expertise. We actually formalized that concept in that we have - we reviewed all the structure of the research within the center, and the bottom line decision was, since the primary responsibility of the scientist is their product expertise, we left the scientists in the "silo" of their product expertise, as far as a formal organization. However, we also recognized exactly what you were saying, that if you look across the center, as with the cell substrate effort, our genomics/proteomics group, these are people represented across the center. And there actually has been developed a formalized grouping called The Scientific Expertise Teams, where these groups are - the people have been assigned, or actually self-designated, and based on their expertise have been grouped together formally in these groups. And we're

in the process of assigning, if you will, a team leader across product expertise to make sure that these are facilitated, these communications, so we had the same exact concept because of the limited numbers of people we have to take care of - to use the sort of leveraging even within the center.

I did want to point out, though, there is something in clarification. The majority of the DNA of the Smallpox vaccine regulation occurs in the Laboratory of DNA Vaccines, so what you did see with Hannah was exactly what was said, was her other matrix expertise played a role in there.

As far as the funding, in fact, I think if you look across the FDA, I was just talking with one of the other centers, they're in the process right now of cutting the support to each of their scientists by two-thirds. And I'm talking the yearly supply money, et cetera, because of issues that have occurred in budgeting. In our center, between the valiant efforts to go out and actually create sources of funding in areas that are critical to us, like cell substrate, which is an externally funded program, largely, but it's still a huge issue for us, and through Dr. Goodman's wise money management, we actually are, in many ways, in much better shape

within intramural funding. Now that said, that's sort of like saying that we only have seven or eight holes in the Titanic, and we could have 40, you know. So it is a big concern, and I think we're fortunate with Dr. Von Eschenbach's confirmation, and his understanding of the importance of science leading regulation so it's predictable and accurate, I think given everything else that's going on with the budget, we actually are in some ways oddly optimistic. But it is a huge concern with the center that in order to best manage our science, we need to have a reliable source of funding to do that. But we owe a great deal of thanks to Dr. Goodman, and his wise money management, that we're in the position we're in, actually.

DR. BAYLOR: I also want to just briefly comment on that point, also, because we really don't see it, I mean, the concept of being held hostage, if you will, by these external funding, because this is a partnership. We've established partnership with these external sources, and, in fact, what I presented in my slide, we provide something unique, and that's what we're doing. When we partnered with the NIH on one of the inter-agency agreements, we're trying to facilitate product development in a certain

area. You need things like assay development. We're some of the best to do that, and so it's a partnership, so it does work to our advantage. We really don't see it as sort of a bad thing, not a cross --

CHAIR KARRON: Thank you, Dr. Weir. And last, but not least, Dr. Walker.

DR. WALKER: Good afternoon. I'm Dick Walker, and in the next few minutes I'd like to give you an introduction to the Division of Bacterial Parasitic and Allergenic Products. Our division is really the other product related division, in addition to the Viral Products Division. And like that group, our mission is to ensure the efficacy and the safety of vaccines, as well as to facilitate the development of new technologies that will enable more vaccines to be produced, and also help maintain the vaccine supply.

The scope of Bacterial, Parasitic, and Allergenic Products is fairly large. In this first slide that I'm showing you, with regards to that, you can see that we have to deal with the respiratory pathogens, sexually transmitted pathogens, pathogens encountered by penetrating inoculation, and those have to do with a lot of parasites, Malaria, for

example. In the last six years, the so-called special pathogens have become a very significant issue, and we're concerned with bacillus anthrace, botulinum, as well as plague. In addition to those product types that we have to deal with, we're also very much concerned with diarrhea-causing pathogens, a lot of mucousally trafficking pathogens, we could be looking at submissions related to these various things. Also, as the name of the division implies, we have allergen products, skin test antigen is actually a newer area that we're seeing more and more activity in, is what we call the live viral therapeutic products, or pro biotics, and so we have a diversity of products that we have to deal with.

To face that diversity, we have the division now organized into six laboratories, immediate office I have myself, and I have Deputy Director Blake, and Regulatory Administrative staff, and then we have the Laboratory of Respiratory and Special Pathogens, which I'll get into all of these laboratories a bit more in a few minutes, Laboratory of Micro Bacterial Diseases and Cellular Immunology. The Laboratory of Methods Development and Quality Control, that's a little different than the other five laboratories, in that it's an approach-directed

laboratory, as opposed to being a group of pathogen type laboratory, and I'll explain that a little bit more in a minute. And then the other more pathogen or product-related divisions include the Laboratory of Immuno Biochemistry. A while ago we talked about naming things, that means allergenic products, maybe that's one to think about. But then the Laboratory of Enteric and Sexually Transmitted Diseases, and finally, the Laboratory of Bacterial Polysaccharides.

The people in these laboratories are approximately somewhere in the 80s, like Jerry's figures - these were made up last spring, and so it varies a little bit, but it gives you a pretty good idea. We've got just a little over a dozen principal investigators, and we've got a number of people coming along, possible tenure track people. In addition to those people, we have somewhere in the mid 40s as far as FDEs, and then we have a number of post docs.

These people, you've heard before, are research and reviewers, and so they conduct regulatory review, as well as research. This research could be programmatic, ongoing studies of regulatory processes of some pathogens, or they may

be focused on a specific path, like it turns out that we might need to know the significance of using rabbit or human complement in a particular assay or something like that, so we have to be able to address specific issues as they come up.

Also, because we have experts to help deal with these products, these people are also in demand, as many of you know, to serve outside organizations in one capacity or the other, whether it's NIH, The Gates Foundation, WHO, so forth.

Finally, one of the activities that these people have to do is they have to find outside money, as far as getting their expendable type support. You've got to keep in mind that our personnel are covered by FDA, but a lot of our expendables, and also ability to get post docs comes from funds that we get elsewhere.

I'm not going to belabor some of these points too much, because I think they've already been made one way or another. These researchers are involved in assay development, trying to improve technologies, have the expertise to troubleshoot. A lot of our people can work with the companies sometimes when there's a problem with a product, seems to be getting out of spec, trying to figure out

what's going on. And, also, by gaining knowledge about products and the science associated with the diseases we're faced with, we get a better -- we're better able to anticipate the needs that might be coming up in the future. And, also, fill those knowledge gaps, hopefully ahead of the time that it's needed. And as I already alluded to, provide expert input to the vaccine community, as well as provide guidance for industry.

I've taken this slide that you've already seen at least twice, and so I'm not going to belabor it. Under each bullet, I've shown some examples of things that are going on in our division now, or could be going on just to sort of flesh out those priorities. For example, just the first bullet under develop methods and models, and so forth - development and evaluation of novel vaccination strategies. I mean, we're seeing new things all the time, whether it's DNA vaccines, or now transcutaneous immunizations being used. The technology is changing all the time, so our people have to keep up, and understand these different technologies so they can do the appropriate regulatory role that they have to do.

The final slides I'm going to run through

are similar to what Jerry did, is just the six laboratories, and just give you a flavor for some of the types of things that they're involved in. The Laboratory of Respiratory and Special Pathogens deals with things like Pertussis. In fact, that's the laboratory that it grew out of, but now it has anthrax, and botulinum, and Neisserinia, and DIPHTHERIA is also included in there. And these people - it's a fairly large laboratory, and they're looking at characterizing virulence factors, evaluating mechanisms of gene expression, developing animal models of infection so that these infections can be better studied, like Pertussis and anthrax, and others, identifying and characterization of regulated virulence factors, and studies botulinum work focuses on like toxin entry into nerve cells, and so forth. So there's a variety of studies being conducted here, mostly directed at respiratory and special pathogens.

This is the Laboratory of Methods Development, which, as I said, is not as product-specific as the others, but the focus of this laboratory is to develop means to evaluate, better evaluate the actual vaccine product, itself. And, also, evaluate the human immune response to that

vaccine. And we realized a number of years ago that this was a critical need that applied to a variety of vaccines, so we set this up as a separate effort.

Laboratory of Bacterial Polysaccharides, of course, many of our vaccine products fall into this category, so we've got people studying the characterization of these vaccines, and trying to better understand the antigens themselves, how they're synthesized. Actually, an example of a spinoff of this, we're very excited about is, one of our people was studying how conjugation chemistry works, and he developed a way to more efficiently achieve conjugation chemistry, and this was a procedure right at the time that the Meningitis vaccine program needed it, and the development of Meningitis vaccine for Sub-Saharan Africa, they were able to take this technology and apply it, and this is now being used in vaccine trials, so that's an example of how really basic research, trying to understand a vaccine product, can actually have a spinoff that can be very beneficial. And I'm sure this technology will be applied to other conjugate vaccines.

In addition to that, we have the Laboratory of Micro Bacterial Diseases and Cellular

Immunology, which is studying the unique immune responses that are involved in working with intercellular pathogens. In addition to TB, this group is also doing work with Tularensis, and they also do the regulatory work related to Malaria. In addition to actually studying the immunology of TB, and some of the antigens that might be important in defenses against TB, give another example of an outreach-type project, is this group is now working with the Aris Global TB Foundation, to try to develop tests to predict the ability or the likelihood that a vaccine candidate might induce the coat phenomenon of the inflammatory response that occurs in people who are already infected with TB when they're vaccinated.

The Laboratory of Immuno Biochemistry, the allergenic products that I mentioned, that are trying to standardize various antigen products. That's a very big need in that field, trying to develop better potency assays for allergenic products, as well as identify contaminates, like endotoxins, for example, that might be in allergenic products, and thus, affect the reaction to these products. And then there's more basic work, trying to understand the immunology of the host, not the

host, but the person's interaction with these products. One type of study is looking at how RSV might affect the sensitivity to asthma, so there's a variety of things going on there.

Finally, the last laboratory that I want to touch on is the Laboratory of Enteric and Sexually Transmitted Diseases, where they're looking at mechanisms of how pathogens work, how they invade, and so forth. But this is a point that somebody, I think Kathy made very early, we're not making vaccines, but we're looking at technologies that might facilitate the development of vaccines, particularly against mucosal pathogens, such as enteric pathogens. One approach is looking at the licensed Typhoid vaccine, TOI21A, and work has been done to show that it can deliver protein and like with polysaccharide antigens in mice, and give protective immune responses, so now various outside groups are looking at how this technology, or this platform might be applied to their various vaccine needs.

So that gives you a quick run through of the types of things that are going on in the Laboratory of Bacterial, Parasitic, and Allergenic Products now, and if there's any clarifications or

questions, I'd be glad to try to answer those.

CHAIR KARRON: Thank you, Dr. Walker. Questions? Okay. Next on the agenda is the open public hearing.

MS. WALSH: Thank you, Dr. Karron. I have not received any request to speak at this open public hearing. Is there anyone in the room who would like to address the committee at this time? Dr. Karron, I turn the meeting back over to you.

CHAIR KARRON: At this time, we're going to take a five-minute break, because this concludes our open session, and we're going to move into closed session. This will allow us to have the room cleared of all the people who should not be here for the closed session.

(Whereupon, the proceedings went off the record at 3:50:19 p.m., and went back on the record at 3:57:38 p.m.)

(Closed session.)