FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

FRIDAY
NOVEMBER 3, 2000

The Advisory Committee met in the Versailles Room, Holiday Inn Bethesda, 8120 Wisconsin Avenue, Bethesda, Maryland, at 8:30 a.m., Robert S. Daum, M.D., and Diane E. Griffin, M.D. Ph.D., Acting Chairs, presiding.

PRESENT:

ROBERT S. DAUM, M.D.	Acting Chair (recused)
DIANE E. GRIFFIN, M.D., Ph.D.	Acting Chair
PAMELA S. DIAZ, M.D.	Member
MARY K. ESTES, Ph.D.	Member
WALTER L. FAGGETT, M.D.	Member
BARBARA LOE FISHER	Member
THOMAS R. FLEMING	Invited Participant
JUDITH D. GOLDBERG, Sc.D.	Member
ALICE S. HUANG, Ph.D.	Member
ERIK HEWLETT, M.D.	Invited Participant
SAMUEL L. KATZ, M.D.	Member
STEVE KOHL, M.D.	Member
JOHN LIVENGOOD, M.D.	Invited Participant
MARTIN MYERS, M.D.	Invited Participant
AUDREY F. MANLEY, M.D., M.P.H.	Member
DAVID S. STEPHENS, M.D.	Member

I-N-D-E-X

P-R-O-C-E-E-D-I-N-G-S

8:30 a.m.

DR. DAUM: Good morning. We will now officially call the meeting to order, please. We will begin our proceedings, since there are some new faces at the table -- at least new to the committee -- by asking each person on the committee and our guests for this meeting to identify themselves and their affiliations, and Dr. Stephens, we will start with you, if that is okay.

DR. STEPHENS: Thank you. I am David Stephens, Emory University in Atlanta, Georgia.

DR. ESTES: Mary Estes, Baylor College of Medicine, Houston.

DR. KATZ: Samuel Katz, Duke University, Durham, North Carolina.

DR. HUANG: Alice Huang from the California Institute of Technology.

DR. KOHL: Steve Kohl, Oregon Health Science University.

DR. DIAZ: Pamela Diaz, Chicago Department of Public Health.

MS. FISHER: Barbara Loe Fisher, National Vaccine Information Center.

DR. GRIFFIN: Diane Griffin, Johns Hopkins

in Baltimore.

DR. GOLDBERG: Judy Goldberg, New York University School of Medicine, New York City.

DR. FLEMING: Thomas Fleming, University of Washington, Seattle.

DR. MYERS: Martin Myers, National Vaccine Program Office.

DR. LIVENGOOD: John Livengood, CDC, Atlanta.

DR. HEWLETT: Erik Hewlett, University of Virginia, Charlottesville.

DR. GEBER: Antonia Geber, FDA.

DR. MEADE: Bruce Meade, FDA.

DR. DAUM: Thank you very much. I am Robert Daum from the University of Chicago. And we will now turn the floor over to Nancy Cherry, who will read the conflict of interest statements and the announcements.

MS. CHERRY: Okay. Before we do that, we have one other person to introduce.

DR. MANLEY: Audrey Manley, Spelman College.

DR. DAUM: Welcome.

MS. CHERRY: Okay, thanks, Dr. Daum. First, I have an announcement. If any of you are here

for a meeting on airbags, I am afraid this is not going to be the meeting you expect. You think I am making a joke, but I understand that information got out on one of our announcement Websites saying -- that was very confusing. Somehow -- and I don't know whether it was man or machine, scanner or human, turned the words a brief into a brief meeting into airbag meeting. So if we caused you any undue stress, I do apologize. I mention this not just because we made a mistake, but because I want to remind you that there are places that you should check to see if there have been any changes in the meeting. Before you get on the plane, it is always wise to tune in to our telephone hotline. And you have in your little packet the page that tells you where to call and see if there have been any last minute changes in the meeting. And I tell this to the people in the audience, because i would always alert the committee members, but I don't know who is coming. So in the audience, if you look at this page, it tells you the phone lines. Also, there is a CBER Website down there. We can usually get information on the phone line and on the CBER Website a little faster than it gets out on the FDA Website.

There have been some personnel changes since this Advisory Committee last met in July. We

have been joined by four new members -- Dr. Diaz, that you met a moment ago, Dr. Goldberg -- Dr. Goldberg on that side -- Dr. Katz down here, and Dr. Manley. And we are delighted to have all of you. We also have suffered a loss. As you probably know, Dr. Harry Greenberg has left the committee because of his new endeavors in the private sector.

Today, we will be chaired by two of the committee members during this transition. We will start out with Dr. Bob Daum. And then for session 2, we have Dr. Diane Griffin.

Here at CBER, Dr. Karen Midthun, whom you will hear from very shortly, has been named Director of the Office of Vaccines, Research and Review. We are pleased to welcome Dr. Midthun back to CBER.

The Committee Management Specialist today you probably met at the front desk or maybe here in the room. It is Denise Royster and Rosanna Harvey. We have a full agenda today, beginning with the update on TSE issues. By the way, this topic is on the agenda for information only. This is not meant to be a committee discussion.

And now I will go ahead and read the conflict of interest statement. The following announcement addresses conflict of interest issues

associated with the meeting of the Vaccines and Biological Products Advisory Committee on November 3, 2000, for the discussion of the safety and efficacy of CPDT Adsorbed, the Diphtheria Tetanus Acellular Pertussis Vaccine sponsored by Aventis Pasteur Limited of Toronto, Canada.

Of the committee members, Drs. Kim and Snyder could not be with us today. However, the Director of the Center for Biologics Evaluation and Research has appointed Drs. Thomas Fleming, Erik Hewlett, John Livengood and Martin Myers as temporary voting members for the discussion.

To determine if any conflicts of interest existed, the Agency reviewed the submitted agenda and all financial interests reported by the meeting participants. As a result of this review, the following disclosures were made. In accordance with 18 U.S.C. 208, Dr. Goldberg, Kohl, Fleming and Hewlett have been granted waivers which permit them to participate in the committee discussion and to vote. In accordance with the Food and Drug Administration Modernization Act of 1997, Section 505, Drs. Estes, Goldberg, Kohl, Stephens, Fleming and Hewlett have been granted waivers which permit them to participate fully in the committee discussions. Dr. Robert Daum

has recused himself from the discussion on CPDT Adsorbed.

Drs. Estes, Faggett, Griffin, Katz and Stephens have associations with firms that could be affected by the committee discussions. However, in accordance with 18 U.S.C. 208 and Section 2635.502 of the Standards of Conduct, it has been determined that waivers or appearance determinations are not warranted for this discussion.

In the event that the discussions involve specific products or firms not on the agenda and for which FDA's participants have a financial interest, the participants are reminded of the need to exclude themselves from the discussion. Their recusals will be noted for the public record.

With respect to all other public meeting participants, we ask in the interest of fairness that you state your name and affiliation and any current or previous financial involvement with any firm whose products you wish to comment on. And we ask that you do this each time you come to the microphone. Copies of all waivers addressed in this announcement are available by written request under the Freedom of Information Act. Dr. Daum?

DR. DAUM: Thank you, Nancy. We will now

move into the body of the meeting proper, and begin with Session 1, which is an FDA presented update on TSE issues, and I ask Dr. Midthun to lead the charge.

DR. MIDTHUN: Good morning. I am going to give a brief update on TSE issues as they relate to vaccines. As this committee knows, there was a joint meeting between this committee and the Transmissible Spongiform Encephalopathy Advisory Committee this past July. The issue for discussion was vaccines that had been manufactured with bovine-derived materials that had been obtained from countries where BSE was known to exist or where the BSE could not be assured not to exist.

The risks of these vaccines were discussed by the committee, and the conclusion was that the risks of acquiring variant CJD from these vaccines was theoretical and negligible.

The joint committees recommended that the materials that had been obtained from countries on the UST BSE list be resourced from other sources. And this pertained in particular to the production of vaccines, that is the routine production, and also to working bacterial or viral master seeds or working cells banks that have been established in the presence of such materials, that these should also be rederived. They

also recommended that there be public disclosure of these issues.

Since that time, Center for Biologics has been working closely with the manufacturers as they implement the recommended changes, and we have also been in the process of drafting a disclosure document and addressing the issues surrounding disclosure, which of course includes coordination with other public health agencies. We hope in the near future to have a document ready for publication in MMWR and also to have additional information available on a Website. Thank you.

DR. DAUM: That was certainly a concise update. We have time for a question or comment from the committee.

DR. MIDTHUN: Keep it very short, they have not been screened.

DR. DAUM: Okay, some very short questions and comments from the committee. Dr. Katz?

DR. KATZ: A reference for the committee, if they haven't seen it. There is a very good one-and-a-half page summary in the current issue of vaccines by Philip Minor and David Saltzbury looking at the issue of vaccines and variant Creutzfeld-Jacob disease that I think would be very helpful. If there is going

to be public disclosure and a statement, I would hope that reference would be included.

DR. DAUM: Thank you, Dr. Katz. There being no further question or comment, I will, as mentioned, recuse myself at this point and Dr. Griffin will take over the chairly duties.

DR. GRIFFIN: All right. We can now move on to Session 2, which will begin with an introduction by Dr. Bruce Meade from the FDA.

DR. MEADE: Okay, getting the technology correct. Good morning, my name is Bruce Meade. I am the chair of the CBER licensing committee that has been reviewing the application that is under review today.

I wanted to start with a very brief introduction this morning, and I want to try to accomplish three things in this introduction. First is to provide a brief background to the file. Secondly, I want to introduce some of the specific issues on which we will be seeking Advisory Committee feedback today. And then third and lastly, I will read through the specific questions for the committee.

So to get started, the product under review today is a diphtheria and tetanus toxoids and acellular pertussis vaccine absorbed or DTaP from

Aventis Pasteur Limited in Toronto, Canada. At the time the application was submitted, they were known as Connaught Laboratories limited. So some of you may recognize the product under that name. And it is for the requested indication for primary series at 2, 4 and 6 months of age with a fourth dose at 15 to 20 months of age, and at this time the sponsor has not requested a fifth dose indication.

I just wanted to review briefly the key milestones for this application. It was submitted in May of 1996. The first CBER review letter was issued on May of 1997. The response from the sponsor was considered complete in September of 1999. We did the preapproval inspection in November of 1999. The second CBER review letter was issued in March of 2000. The response from the sponsor was considered complete in August of 2000, and we are now here in November of 2000 at the Advisory Committee.

I should mention that there was a corresponding establishment license amendment, for which there are no outstanding issues. And I should note that the DT vaccine, the diphtheria tetanus toxoid vaccine from Aventis was licensed in the U.S. in 1997.

Again, the acellular pertussis component

of the product contains 5 antigens which are listed here -- inactivated pertussis toxin, and I use the abbreviation IPT for inactivated pertussis toxin, filamentous hemagglutinin, pertactin, formerly known as 69K outer membrane protein, and a preparation that contains both times of fimbriae, types 2 and 3. The composition contains approximately equal amounts of both types of fimbriae. But to avoid confusion in some of the slides later, you will note that the antibodies to fimbriae are measured in a single assay which uses as an antigen a mixture of both types of fimbriae. So you will be seeing results from four antibody assays for these five particular components.

There are two DTaP formulations that have been evaluated clinically. There is the CPDT, which -- and again, some of the literature and some of ours was called the classic formulation, which is a low dose formulation. I will review that in the next slide. And that is the product covered under this application. They have also submitted data on a product that they have called HCPDT, again sometimes called the hybrid formulation, which has higher quantities of inactivated pertussis toxin and FHA. And the specific composition is shown on this slide. Again, it indicates the specific quantities of each of the

antigens. The adjuvant is aluminum phosphate and the preservative is 2-phenoxyethanol. And you will note that the hybrid formulation, the higher dose formulation, differs in inactivated PT and FHA, and it contains twice as much PT and four times as much FHA. And again specifically to note that the PLA is for the CPDT formulation.

And again, we will hear much more about these and specifically from the manufacturer sponsor shortly. But I wanted to briefly outline the two efficacy studies that have been submitted in support of this application and that the two APL DTaP vaccines have been evaluated in two efficacy trials sponsored by NIH in the National Institute of Allergy and Infectious diseases.

The first trial we will call Sweden Efficacy Trial I, which was done in 1992 through 1995. It used the CPDT formulation. And the second trial, Sweden Trial II, from 1993 to 1996, that used the higher dose formulation.

Again just to briefly outline Trial I. It was a randomized, double blind, placebo-controlled trial using an immunization schedule of 2, 4 and 6 months of age. The study vaccines were CPDT and a two-component DTaP vaccine from SmithKline Beecham. It is

important to note that this is an investigational product. It differs in composition from the SmithKline Beecham three-component vaccine or Infanrix that is licensed in the U.S. The Infanrix contains a third component, the pertactin component, so it differs from this investigational product. The study included two control vaccines, a whole cell control vaccine from Aventis U.S., formally Connaught Labs, and the diphtheria tetanus toxoids was used for establishment of estimates of absolute efficacy. So it actually was not a placebo-controlled trial because the inactive control for pertussis was a diphtheria tetanus toxoids vaccine.

There were approximately just over 2,500 infants per arm of the study, and the follow-up was approximately 24 months after the third dose. The case confirmation in this trial was through culture, serology or epidemiologic linkage to a confirmed case. The efficacy results for the CPDT vaccine are shown here using the WHO definition, which was laboratory confirmed pertussis with at least 21 days of paroxysmal cough. The estimate of efficacy was approximately 85 percent with a confidence interval as indicated. They also -- one of the other definitions was for mild pertussis, which again was laboratory

confirmed, with at least one day of cough, and it had an efficacy of approximately 78 percent. And there was no evidence of loss of efficacy during the two-year blinded follow-up.

Now the second trial, Trial II, was also randomized, double blind trial. But this trial, the efficacy was evaluated relative to the whole cell pertussis vaccine included in the trial. There was no inactive control. The immunization schedule for the majority of the subjects were the 3, 5 and 12 month schedule. There was a subset of approximately 12 percent of the subjects that were evaluated on a 2, 4 and 6 month schedule to do some schedule comparisons. The study vaccines were the HCPDT vaccine, which again is the higher dose formulation, the five-component product from Aventis. They also included the same investigational two-component vaccine from SmithKline, a three-component DTaP from Chiron, and the control vaccine was a whole cell vaccine from Medeva in UK. This study was a much larger study, approximately 20,000 infants per arm, and the follow-up was approximately 22 months after the third dose.

In this trial, because it was a much larger trial, they didn't do the serologic confirmation. It was culture only for case

confirmation. And the efficacy results for typical pertussis, which again is culture-confirmed pertussis with at least 21 days of paroxysmal cough -- again, it was a relative efficacy trial and it was concluded to be comparable to the whole cell control vaccine with a relative risk of 0.85 with confidence intervals indicated.

Given this very brief introduction, I wanted to now spend the next few minutes again highlighting a few specific points that we will be seeking Advisory Committee input on. And the first -- to indicate that the specific issues on which we will be seeking Advisory Committee input are listed here. We will be asking for feedback on efficacy of CPDT for the requested indication, safety for the requested indication. We will be asking for feedback on concurrent administration of this vaccine with other pediatric vaccines routinely recommended for infants and toddlers. And we will be asking for comment on post-marking studies should it reach -- the vaccine reach approval.

And now again I wanted to mention a few specific issues. One started with a general question that will come up I think both in the context of the efficacy discussions and the safety discussions, and

that concerns the applicability of data from the hybrid or the higher dose formulation to the product for which we are seeking licensure, the CPDT. Again, the data from the hybrid have been submitted in support and clearly they are relevant for many questions under discussion. Because the manufacturing process for the antigen concentrates is the same for both products. The composition, as we showed earlier, is certainly very similar, but is not identical because it has higher inactivated PT and FHA.

Again, in the primary efficacy study, the immunization schedule was different for the two vaccines. Again, the schedule -- the 2, 4 and 6 month schedule in Trial I versus the 3, 5 and 12 for Trial II. And again, the design of the efficacy studies was different. With the first trial, it was designed to assess absolute efficacy and in the second trial was to assess relative efficacy. So, again, given these differences, throughout our discussion there will be questions on applicability to the product -- of the hybrid for the product we are seeking licensure.

And then I want to point out one very -- in a little bit more detail a specific question that will be -- that we wish to discuss in more depth and I will discuss this in more depth later. But I wanted

to highlight it first as we start the morning discussion. And that concerns some data gained from the U.S. Population Bridging Study. This was a study done in the U.S. that was conducted to compare antibody responses between infants in the U.S. and Swedish infants from the efficacy study. The goal was to provide immunogenicity data to support the generalization of the Swedish efficacy data to the U.S. infant population.

The study in the U.S. was a randomized blinded comparison of two lots. It was CPDT lot 6 and lot 9. Lot 6 was the lot actually used in the efficacy trial, and it is important to note that that was approximately four years of age at the time that it was entered in the U.S. Bridging Study. And because it was an older lot at that time, they also included a more recently manufactured lot, lot 9.

And then the analysis of that was done in the head-to-head comparison in the laboratory. They compared post-dose 3 antibodies to the pertussis antigens in sera from infants immunized with lot 6 from the Sweden Trial I, lot 6 from the U.S. Bridging Study and lot 9 in the U.S. Bridging Study.

Serology data was submitted to us for review in August of 1999, and the observation is that

the protectant antibody responses did not meet APL defined criteria for either lot when compared to lot 6 in Sweden Trial I. And this was seen both in the lower geometric mean concentrations in the U.S. infants, a higher proportion of U.S. infants that were non-responders and a higher proportion of low responders in the U.S.

Again, this showed -- this is washed out a little bit. This shows -- is that visible at all? I am sorry, the data are shown here as reverse cumulative distribution curves for the four antibody assays -- PT, FHA, fimbriae and the pertactin. The lower right-hand corner shows the results for the pertactin. And for the three other -- and again, just to introduce you, these are reverse cumulative distribution curves which were scanned in from the sponsors submission. The vertical axis in all of these is percent going from zero to 100 percent. And the horizontal axis is ELISA titers and it is showing the proportion of individuals who had an antibody titer of at least equal to that value. You will see for the three antigens, PT, FHA and fimbriae, there are again some differences, but they are very similar in shape and in magnitude for the three. But in the pertactin, they are very different. That one is shown larger on

this slide. And you will see the darker line at the right is the -- again, all of these were done in the same lab at the same time. These are the sera obtained from the Swedish Trial from infants in the trial. And then the data from the two U.S. lots are shown in these other two lines. And what you will see is that there is clearly a difference in the shape of the curve, again highlighted at the lower end of the curve. And again we will be coming back to this in more depth. But this is an observation that led to a regulatory question which is listed here, and that the lower responses to an antigen believed to be important for protection suggest that the vaccine may have a lower efficacy in the U.S. population than that estimated for the efficacy trial in Sweden. And again, the manufacturer and again in our presentation later will discuss the various data that address this issue. And again, this is an area that we will be seeking feedback from the Advisory Committee.

And again I wanted to mention very briefly some of the -- when Dr. Antonio Geber, the clinical reviewer, makes her presentation later, some of the points that she will be making and, again, some of the specific areas where feedback will be requested from the committee. I just wanted to mention them very

briefly here. One is that there was observed increasing rates of local reactions following the fourth dose, which has been seen with others of the DTaP vaccines. But again, we wanted to show this data specifically for this product. We will be reviewing the rates of hypertonic hyper-responsive episodes called HHE in the trials with the hybrid vaccine. We will be reviewing the safety and immunogenicity data for concurrently administered vaccines and will note that data are not currently available for all of the routinely administered vaccines. And again, we will briefly comment on the data base for toddlers who received the fourth dose prior to the age of 17 months. Again, in the fourth dose data base, there are relatively few children below the 17-month age group.

And given that, again, very brief introduction, some of the general questions I wanted to read through before the sponsor presents the specific questions for the committee today. Again, I will just read them through at this time. Question 1 will be asked in two parts. The first is, are the data adequate to support the efficacy of the acellular pertussis component of CPDT when administered to infants and children in the U.S. as a four dose

series? If not, what additional information should be requested? And if the answer to the first part is a yes, we will ask the committee to discuss the adequacy of the data to support the efficacy of the acellular pertussis component of CPDT when administered to infants in the U.S. as a three dose series.

Question 2 will be, are the data adequate to support the safety of CPDT? Please specifically address both the infant series and the fourth dose data. And if not, what additional information should be requested?

Question 2, please discuss the adequacy of the data to support the concurrent use of CPDT with other vaccines administered according to the recommended schedule of infant and childhood immunizations. Please discuss additional information, if any, that should be requested.

And question 4 is please identify any issues that should be addressed by post-marking studies. That concludes the introduction. I will turn it back to the chair.

DR. GRIFFIN: Okay. Questions on this introductory presentation? Any questions from the committee? Dr. Huang?

DR. HUANG: What is known about the

immunogenicity studies of currently used pertussis vaccines? You said that not all the information was in, but there must be some.

DR. MEADE: Oh, yes. This will be reviewed in detail both by the sponsor and by Dr. Geber later. The data that are available will be reviewed in detail. But there are some -- the current data don't cover all of the vaccines currently in use. And again, that will be reviewed in detail and be discussed later following those presentations.

DR. GRIFFIN: Dr. Katz?

DR. KATZ: You highlighted the discrepancy in pertactin antibodies, and yet if I am correct, we have a licensed vaccine that has no pertactin. Is that not correct? John Robbins' vaccine has no pertactin, it is only pertussis toxoid.

DR. MEADE: The answer is yes. But the data for each product is being evaluated on its own merits based on the efficacy. We have data for their product and their antigens as formulated, and the efficacy data was evaluated for the full -- the vaccine as formulated and described here. And in order to generalize or compare the data in the U.S., the best tools or the only tools available are to look at immunogenicity in the U.S. population. And when you

see a difference, it makes it difficult to -- again, to generalize the data from the efficacy study and apply it to the U.S. population. So, again, I think the question you are bringing up I am sure will be covered in much more depth as the morning discussion proceeds.

DR. GRIFFIN: Other questions? Yes, Dr. Fleming?

DR. FLEMING: I guess that kind of opens the door at least for a comment relating to uncertainty about correlates of immunity. With that two-component vaccine, we have this paradox that the overall antibody responses to FHA and PT were much higher than, for example, in Sweden Trial I with the five-component vaccine. So even though that two-component vaccine didn't have a pertactin component, it had particularly high antibody responses for FHA and PT. On the other hand, its efficacy was lower than the five-component vaccine that had much lower antibody responses for FHA and PT. And kind of leading into comments that are going to trouble me throughout the day, which is we are having to rely on serologic evaluations and antibody levels and what is it that we need to achieve to be confident that that gives us adequate evidence of efficacy.

DR. GRIFFIN: Okay. I think that that sort of sets the stage for what we are going to really discuss in much more detail and what the issues are going to be. One further comment before we move on to the sponsor's presentation. Please turn off your cell phones if you have them or put them on vibrate. It is very disruptive to the overall proceedings to have them going off. Thank you.

Now we will move on to -- if my docket is correct -- Ms. Marie Minchella.

MS. MINCHELLA: Good morning, Dr. Griffin, Advisory Committee members and the CBER Review Committee, ladies and gentlemen. My name is Marie Minchella. I am from Regulatory Affairs at Aventis Pasteur. And on behalf of Aventis Pasteur, we wish to thank Dr. Meade for his opening remarks and for the invitation to present our CPDT vaccine to the Advisory Committee today.

CPDT vaccine is a sterile suspension of five-component pertussis vaccine combined with diphtheria and tetanus toxoid and adsorbed to aluminum phosphate. And the indication which we are seeking license for is for the primary immunization at 2, 4 and 6 months of age and a booster dose at 15 to 18 months. I won't go into this slide. Dr. Meade has

taken the task and has gone through the composition of our product, so I will move on.

CPDT vaccine adsorbed was researched and developed and is manufactured at Aventis Pasteur Limited. As Dr. Meade had indicated, we did receive a license in the U.S., but we have been producing and marketing diphtheria tetanus since 1977 globally.

We received our first license in Sweden early in 1996, and then this was followed by our Canadian license in December. In the same year, we had submitted a license application to the U.S. However, due to intellectual property conflict, this was delayed for pursuing it further. This has just been recently resolved and we are pursuing many other various markets for license applications, and especially the one in the U.S. has been reactivated.

This product has been licensed in 23 countries globally under the trademark name of Tripacel, and we have been marketing over 2 million doses of this product.

CPDT base combination vaccines remain the vaccine of choice in Canada. The current care in Canada includes an IPV and a Hib vaccine for childhood immunization. Five months following our CPDT license in Canada, we received two product licenses, Quadracel

and Pentacel, which contain the Hib and the IPV components. These products have been used exclusively across Canada for the last three years, where we have marketed over 5 million doses.

We have brought many experts with us today to answer your questions. In consideration of time, we have limited the presentation to two speakers. We will start with a manufacturing and clinical overview with Dr. Fahim followed by Dr. Decker, who will give the efficacy and safety data. And then Dr. Fahim will return to the podium to discuss immunogenicity and concomitant information with you and concluding remarks. The Aventis Pasteur team, which we have with us today are Drs. Mills and Wubbel from clinical, Mr. Phong Xie, biostatistics, Ms. Lucy Gisonni-Lex and Dr. Pat Pietrobon, clinical serology. Unfortunately, Dr. Patrick Olin, who was the independent principle investigator from Sweden, was unable to join us today. However, we have made arrangements to connect him through teleconferencing for any questions you may have for him, as well as Dr. Scott Halperin, the principle investigator for many of our Canadian studies. Harold Hebble is also available through teleconferencing today, and he was the epidemiologist and safety monitor for Sweden Trial II.

Just two points that I would like to raise at this time. Some of the slides do have the former corporate identity identified because these slides have been taken from publications. So that data may reflect Connaught Laboratories.

The other point that I would just like to make right now is that in your handouts in the pre-read, the confidence intervals for some of the data that we are presenting have been identified there. We have taken them off the slides due to just the mass amount of information that we are presenting today. On that note, I would like to turn the podium over to Dr. Fahim.

DR. FAHIM: Thank you, Marie. Good morning, ladies and gentlemen. Thank you for the opportunity to discuss the CPDT vaccine with you. What I will be doing is over the next few minutes just cover the manufacturing and clinical overview.

For the manufacturing overview, I want to start off by telling you why we have the five components that we have in the vaccine. So in essence the rationale for including all of those five components. We start off with the PT and FHA, and these two antigens were identified early on as very important for protection against pertussis in the

acellular vaccines. They were shown to be protective in animal models of protection and they were also included in human clinical trials and were actually included in Japanese vaccines in the early 1980's. They promote attachment of bacteria to ciliated epithelium. We also included pertactin, and this antigen was shown to be protective in animal models as well and also promotes attachment of the bacteria to ciliated epithelium.

We have a unique feature in our vaccine, which is a fimbriae 2 and 3, and we included those two components here because from early vaccines in the early 1950's, where the vaccine manufacture had antigen 2 or fimbriae 2 in their vaccine, and that protected against Type II associated disease but did not prevent Type III associated disease. The reverse was also true in other instances. Because of data like this, the WHO has mandated that all whole cell vaccines should include both fimbriae 2 and 3 in their composition. Fimbriae 2 and 3 also inhibit pertussis colonization.

Now I would like to go through the manufacturing process flow. And we start with the fermentation of the bacterium and then we segregate the fermentation broth into supernatant and the cells.

From the cells, we obtain fimbriae 2 and 3, and from the supernatant, we obtain the other antigens.

From the supernatant, we get a chromatography step by which we purify the three antigens. We start off with the pertactin or 69K, and we purify that antigen and then adsorb it separately to aluminum phosphate. We then get the pertussis fraction where it is purified. And then we detoxify using glutaraldehyde and then we adsorb it also to aluminum phosphate. And finally, we get the FHA fraction where it is purified and then chemically treated with formaldehyde to detoxify any potential pertussis toxin in that fraction. And then we adsorb it to aluminum phosphate as well.

From the cells, as I mentioned earlier, we get the fimbriae 2 and 3 and purify them and adsorb them to aluminum phosphate. As you can see, we have all of the fractions separately purified and adsorbed.

For the diphtheria and tetanus, we ferment the diphtheria, purify it in concentrate and detoxify and then adsorb it to aluminum phosphate. And for the tetanus, we ferment, detoxify, purify in concentrate and then adsorb it to aluminum phosphate. With those antigens then, we get those six fractions here, all concentrated and all adsorbed to aluminum phosphate,

which then allows us to pool them to formulate the CPDT vaccine. We end up with adding additional aluminum phosphate to make up to 1.5 mg of aluminum phosphate, and then we add 2-phenoxyethanol to get the CPDT vaccine.

This is the composition here, and I am not going to go through this in detail. You have seen it already by Dr. Meade and earlier on. One point of consideration here, we have 2-phenoxyethanol here as opposed to thimerosal. From the beginning, this vaccine was intended with combination with IPV. And because of that, because of the compatibility of the IPV and the thimerosal, we opted to use 2-phenoxyethanol. You have seen this composition of the HCPDT as well, which has been used in Sweden too.

This is the manufacturing experience we have to date. As you can see, we have extensive experience to date with this vaccine and we have manufactured over 40 lots at scale of the CPDT vaccine for which we are seeking licensure. We also formulated 50 lots of Pentacel that is being used in Canada exclusively.

I would like to now give you a brief overview of the clinical development plan and experience we have. This here is a very busy slide,

but it shows the overall experience that we have with this vaccine for phases I, II and phase III. You will notice that many of those trials were conducted under U.S. IND. Because of the busy nature of this slide, we have now segregated them into phase I here. You can see we had five trials for children and toddlers for safety and immunogenicity of the vaccine. This was then followed by phase II trials. Many of those were conducted at 2, 4 and 6 and also 2, 3 and 4. These trials were conducted for lot consistency as well as safety and immunogenicity of the vaccine. Many of those trials in the children in those trials went on from a 2, 4 and 6 primary immunization and got the fourth dose booster with this vaccine.

We had two efficacy trials conducted, Sweden I and Sweden II referred to earlier by Dr. Meade. I am not going to dwell on them. Suffice to say that for Sweden I, we used CPDT vaccine. For Sweden II, we used HCPDT vaccine in two schedules here. And then we finally conducted a U.S. Bridging Trial, again referred to earlier by Dr. Meade.

This is the overall experience in terms of the number of subjects and doses used. I am not going to go through all of the numbers. You can see that we have extensive experience in human clinical trials

with about 81,000 doses used to date in clinical trials for either the CPDT formulation or the HCPDT formulation. In addition, we have also 15,000 doses that have been administered with other combinations in other clinical trials.

With that introduction, I would like to then turn the podium over to Dr. Decker, who will be talking about the safety and efficacy of the vaccine.

DR. DECKER: Thanks Raafat. It is a distinct and unexpected pleasure to be here today. Until a few weeks ago, I was happily ensconced in Vanderbilt, where my colleagues and I at Vanderbilt had the pleasure of participating in the very first clinical trial of this vaccine, and I never expected I would be here, not only at the beginning, but able to participate in what I hope is the culmination with this vaccine.

I would like to cover a couple of things for you. First, the safety issues. I would like to show you the frequency and severity of the common adverse reactions and compare them to this vaccine, both to whole cell vaccine and to other acellular pertussis vaccines. I would like to show you the risk of serious or severe adverse effects. And finally, I would like to show you the consistency of the safety

of this vaccine as evaluated across multiple studies and multiple populations.

That first trial of this vaccine that I alluded to was organized by the NIAID and known as the Multi-Center Acellular Pertussis Trial. And our goal in that trial was to put into one head-to-head competition every acellular vaccine then under development around the world. And we succeeded in getting all but one. We got 13 vaccines. Two mono-component vaccines containing PT only, four two-component vaccines containing PT and FHA, including the one licensed in the U.S. as Tripedia, three three-component vaccines containing PT, FHA and pertactin, including the one licensed in the USA as Infanrix, two more three-components that contained fim instead of pertactin, and those aren't licensed anywhere, and then two vaccines with four or five components, including Acel-Immune and the vaccine we bring you today.

I would like next to show you the safety comparisons -- the adverse reaction comparisons out of the multi-center trial. And for each of these slides, the right-most bar represents the reactions that occurred with the Lederle whole cell vaccine, which of course is one of the two U.S. whole cell vaccines in

commercial distribution.

73 percent of the whole cell recipients had injection site redness, about a quarter to a third of them falling into the severe category, as compared to 26 to 39 percent of the acellular recipients, a far lower proportion of whom had the more severe reactions. This is the pattern we saw with all the adverse reactions. A dramatic reduction in both frequency and severity with the acellular vaccines. 60 percent of the whole cell recipients had injection site swelling, nearly half of it severe, as compared to 16 to 30 percent of the acellular recipients. 60 percent of the whole cell recipients had fever of 100.1 or greater, about a third of them falling into the or-greater category, as compared to 18 to 31 percent of the acellular recipients, of whom few or none had severe fever. Fussiness of moderate or severe level was recorded for 41 percent of the whole cell recipients compared to 12 to 19 percent of the acellular recipients. And injection site pain was seen in 40 percent of the whole cell recipients, of whom nearly half had severe pain, as compared to 4 to 11 percent of the acellular vaccine recipients.

You will notice that throughout all these slides, the vaccine we bring you today is comfortably

within the range of U.S. licensed vaccines.

As you have already heard, this vaccine was studied or an analogous vaccine was studied in a couple of efficacy trials. I would like to just show you an overview of the 9 or more efficacy trials conducted worldwide after the MAPT. There are six that involved vaccines that are licensed or have been submitted for licensure in the United States and thus are relevant to us. Those six are shown here. The three in blue were organized and financed by the United States Government. The three in black were organized and financed by the manufacturers. All of the U.S. government organized studies but none of the manufacturer sponsored studies were fully double blinded, randomized, prospective and placebo or DT controlled. These two studies were organized by the NIAID as direct follow-ups to the multi-center trial I just showed you, and those two studies had not only the characteristics I just mentioned, but in addition each study featured two acellular candidate vaccines in head-to-head competition. They used in addition to the DT control arm a U.S. whole cell vaccine control arm. They immunized their participants at 2, 4 and 6 months, the U.S. immunization schedule, and they used closely coordinated protocols between the two

countries to enhance the comparability of data.

In the Italian NIAID trial, the vaccines looked at were Infanrix and a vaccine called Acelluvax from Chiron Biocine. I want to focus first on the Sweden I trial conducted in Stockholm, and that study involved four arms. There was the DT control arm. There was a two-component acellular vaccine from SmithKline Beecham. There was the vaccine we bring you today, our five-component vaccine. And there was the U.S. licensed whole cell control arm. Also conducted as part of this trial nested within this overall prospective trial was a household contact case control study that gives us important additional data.

We are going to focus here on safety. In this slide you see the common adverse reactions, systemic and local, at the 2-month, 4-month and 6-month injections for each of the study arms -- DT, two-component, five-component and the whole cell. And what you see here is that within each injection, the rate of reactions is essentially identical for the DT control arm, for the two-component and for the five-component vaccine, and always distinctly less than for the whole cell vaccine. Now the rate of reactions increases from injection to injection, which is a pattern that is typically seen with the acellular

vaccines, but it always remains more favorable than with the whole cell vaccine.

One of the most striking evidences I think of the lack of reactogenicity of the acellular vaccines is this slide out of the Sweden I Trial, which shows the fever occurs for the first 24 hours following immunization for the four arms. And as you see here, the fever occurs for the DT placebo recipients and the two acellular vaccines are perfectly superimposable and distinctly different from the fever curve associated with the whole cell vaccine.

As far as serious or severe adverse events go, here are the data. You see for the five-component vaccine, there were a total of 10 such reported events, which is fewer than with the two-component or with the DT vaccine. None of these numbers, of course, significantly differ from each other. But in most cases, they are significantly lower than for the whole cell vaccine.

Sweden Trial II was organized as a direct follow-up to Sweden Trial I. And its intent was to extend the findings of the Sweden I trial to create a bridge to the companion Italian trial, and that was done by including in this trial the Chiron Biocine

three-component acellular vaccine that was studied in Italy and which was proven in Italy to be 84 percent efficacious.

The intent was also to evaluate the HCPDT formulation. As mentioned before, this vaccine is produced in two formulations, the classic and the hybrid. The classic intended for use in a stand-alone DTaP vaccine and the hybrid intended for use in combination vaccines. A different formulation, a higher quantity of PT and FHA, was included in the hybrid as insurance against any possible interference when combined with other vaccines.

So the intent was to look at that vaccine, and then finally to replace the relatively inefficacious U.S. whole cell vaccine with a European whole cell vaccine of known high efficacy.

So some key things about this study that you have heard mentioned. As they replaced a different whole cell, the fact that there was a decision made not to include a non-pertussis vaccine control arm. Because of the favorable results of the first study, it was felt that all the children involved in this study ought to be offered pertussis vaccine. Therefore, it is not possible, lacking a placebo control arm, to calculate absolute efficacy and one

has to calculate relative efficacy. That is to say the efficacy relative to one of the other arms in the study. And two such calculations are available. The design calculation was to use the whole cell vaccine as the reference, and I will show you those data. But because it turned out unexpectedly that the two-component vaccine from SmithKline Beecham was not very efficacious, it was also used as a reference as a pseudo placebo, and I will show you those data. And finally, the majority of the children, those involved in the efficacy calculations, were immunized at 3, 5 and 12 months, which is the standard schedule in Sweden. A subgroup was immunized at 2, 4 and 6 months to provide a bridge for serologic data back to the U.S. and back to the first Swedish trial.

The fact that the Swedish children are immunized at 3, 5 and 12 offers the opportunity to do an interim efficacy analysis right here in that prolonged interval between the second and third dose, and those data proved to be very interesting.

Here are the severe and serious adverse events as recorded in the Sweden Trial II. This is the two-component, the three-component from Italy, and the five-component vaccine from Aventis. You will notice that once again we see for most of the adverse

reactions very similar rates among the three acellular vaccines and distinctly less than in whole cell for those reactions that are clearly attributable to vaccination. For those reactions that are recorded but in many cases are not related to vaccination, the numbers are much more similar as you would expect.

Two categories of adverse reaction of particular interest, and I will show you those in detail. One is HHE, where the rates and numbers are considerably higher than seen before. And then deaths, I will show you the line listing of. With respect to HHE, in Sweden Trial I, HHE was not prospectively defined. In fact, the investigators -- it was an unexpected event for the investigators. Whole cell vaccine hadn't been used in Sweden for nearly -- I think more than a decade. And the occurrence of a couple of cases of HHE in the first trial startled the investigators and it caused them to focus with particular intensity on this question.

So in Trial I, the cases that are reported were identified retrospectively because they were reported as having these characteristics -- pallor, hyporesponsiveness or lack of muscle tone. In Sweden Trial II, special meetings were held with the physicians and nurses to emphasize prior to the

study's initiation the detection of HHE. And HHE for this trial was prospectively defined as diminished or absent response to stimulation or lack of muscle tone. And finally at each visit, the parents were questioned regarding the occurrence of any such signs or symptoms.

This vigorous attention -- we are going to need to go back a slide in just a moment -- this vigorous attention to these definitions had a result that is clear here. What I am showing you are three companion trials, Sweden I, Sweden II and Italy. For the two-component SmithKline Beecham vaccine, the rate of HHE in the Sweden Trial was zero. There were 22 cases for a rate of .36 in the Sweden II. Similarly for our vaccine, there was only one HHE in the first trial and there were 29 in the second trial. For the Italian vaccine, which only had one HHE in the Italian trial, there were 16 recorded for a rate of .26 in Sweden Trial II. And the similarity of definitions between Sweden I and Italy is shown by the very similar rates of HHE for the whole cell that was a common vaccine in those two studies.

Could you go back one, please? Because of the questions that were raised about HHE and these characteristics I have just shown you, the principle

investigator for this study was asked about this and the quote that he provided is shown here. Patrick said, "The difference in numbers of HHE's in Trial I and Trial II is mostly related to the awareness after the experience in Trial I. Before Trial II, 20 investigators involved in the trial briefed all the nurses specifically about HHE and the parents were specifically alerted to the possibility of extreme weakness after vaccination." "And accordingly," Patrick says, "I believe that the number of HHE's in Trial II shall be higher than in Trial I, and this may partially reflect over-reporting."

So indeed that is the pattern we see here. What we conclude from these data is that the distinctive aspect about HHE is not the vaccines, but rather the study, which stands alone in pursuing this question so vigorously.

Now I promised you data on the deaths reported in the study, and here they are. There were a total of 12 deaths reported in all of the studies. Two children in phase II trials died. Those deaths were categorized as SIDS. They were respectively 5 and 22 days after immunization. And then in Sweden II, which was a very large trial with very long follow-up, there were a total of 10 deaths recorded during the

time of the trial, the closest of which to immunization was a month later. And the most common cause of death recorded for any of these was SIDS, but there were a variety of other causes of death.

Next I would like to show you the adverse reaction data from the phase II trials that were conducted following these efficacy trials. For the next several slides, there is going to be a common pattern. On the left-hand side of the slide, I am going to show you data from the phase II trial that was designed to compare the five-component vaccine with whole cell vaccine. And on the right-hand side, I will show you data from the phase II trials that are designed to compare the two formulations of the five-component vaccine. What you will see for all these slides is that consistently the five-component vaccine is much less reactogenic than whole cell and the two formulations are functionally identical.

This slide looks at fussiness. And once again we see the pattern that was seen at the MAPT, a nearly two-fold reduction in the occurrence of fussiness, a reduction in its severity for the five-component as compared to whole cell. And we see for the comparison of the two formulations, classic and hybrid, virtually identical responses. Let me comment

also that for some of these adverse reactions, there were slight differences in the definitions from study to study. If they are different, I show them each here. And if it matters, I will call it out to you.

Here is injection site tenderness. We see the same pattern as before, a distinct reduction as compared to whole cell and the equivalence of the two formulations. Injection site swelling, the same pattern, distinct reduction as compared to whole cell and the equivalence of the two formulations. Injection site redness, the same.

Fever -- now here is a place where it matters. It turns out that this slight reduction in the lower limit of fever recorded for the phase II C studies had the effect of sweeping in to the febrile group a very large number of almost normal children. So the lowest level of fever here is a much larger group for this study. Apart from that, you see that we preserve the same pattern as before. A distinct reduction compared to whole cell and equivalence of the two formulations.

Next we come to the U.S. Bridging Study. And because this was not a comparative trial, I don't have a nice comparative block to show you. But what we have done here is we have scaled the graphs to the

same scales as previously. So if you remember the previous slides, you will recognize that these results are all consistent with what I have shown you before. Low levels of these adverse reactions -- redness, swelling, fever, tenderness, pain and irritability.

Let me turn now to the question of safety of the fourth dose booster. I apologize for the quality of this. This is scanned out of Mike Pichichero's paper reporting the results of the extension of the Multi-Center Acellular Pertussis Trial which looked at the fourth dose booster, and this provides useful comparative data comparing this five-component vaccine with all of the other acellular vaccines, including those licensed in the U.S. -- three of the four licensed in the U.S. As was noted by the authors here, "A significant variation in prevalence among the 12 acellular vaccine groups was observed only for redness and swelling." And then among the whole cell groups for fever. I am not going to show you that one. I am going to show you the redness and swelling. There was a significant difference for the acellulars. Now because this is impossible to read, I have flagged for you the columns that belong to the five-component vaccine. This is the redness slide. These are the children who got three

doses of acellular followed by a booster of acellular. These are the children who got three doses of the whole cell followed by a booster of acellular. And you see for redness for both sequences of vaccination, the five-component vaccine is in the middle of the pack. Similarly for swelling, the same result is observed. And as noted, those are the only two for which the acellular vaccine sequences differed significantly in their rates of adverse reactions.

Now I will show you the data from the phase II trials. Again, the same pattern of slides as shown before. Here is the fever comparison. This is for the booster dose now. 63 percent of the kids boostered with whole cell had fever of 37.5 or greater as compared to 10 percent of the five-component acellular recipients. And again, the same difference in definitions of the lowest level of fever. But again you see comparability between the two formulations of the five-component vaccine. We see the same pattern here for fussiness. We see for injection site redness and for injection site swelling that the more favorable reaction profile for the acellular vaccine persists.

Now you will notice that the advantage of acellular over whole cell is not so marked here as for

the other reactions, and that is a pattern that has been observed commonly that the acellular vaccines have relatively -- that the adverse reactions with the acellular vaccines more closely approximate those of whole cell, although they always remain more favorable with increasing number of injections. One important thing to note though is that this more marked redness and swelling with the acellular vaccines at the booster dose is not associated with pain. It is largely a painless swelling that doesn't interfere with function or activity and that is shown quite clearly here where 86 percent of the whole cell recipients had injection site tenderness with a substantial proportion, well more than half, being moderate or severe as compared to 23 percent of the five-component vaccine recipients. Once again we see that the two formulations perform identically.

So in summary, with respect to the common adverse reactions, they are reduced in frequency and in severity for both formulations of the five-component vaccine as compared to whole cell vaccine, both for the primary series and for the booster. The pattern of adverse reactions following the primary series is consistent with that of other U.S. licensed acellular pertussis vaccines. And a consistent

reactogenicity pattern is demonstrated across all the studies -- the NIH comparative trials, our phase II trials, the U.S. Bridging Trials -- between the two formulations of the five-component vaccine.

Let me now review our total experience with respect to the serious or severe adverse reactions. This slide shows adverse events following 11.5 thousand doses of the classic formulation. There was one HHE recorded, and that was in the Sweden I efficacy trial. Five total instances of high fever out of 11.5 thousand doses. Seven convulsions or seizures within 30 days with a very long surveillance period. And then 17 episodes of prolonged crying.

Following the hybrid formulation, almost 70,000 doses, we see a similar favorable safety profile with very few instances of adverse reactions reported apart from HHE in Sweden II, which we have already discussed.

With respect to the booster dose of the two vaccines, for the classic formulation, we have yet to observe any serious or severe adverse events. And for the hybrid formulation, we have observed one HHE so far in about 1,000 doses.

So in summary, for the classic formulation that we bring you today for licensure, serious adverse

events were rare and occurred at a frequency consistent with other acellular vaccines. Only one HHE case was observed in nearly 12,000 doses. For the hybrid formulation, equally severe adverse events were rare, consistent with other acellular vaccines. We observed only two HHE cases in 69,000 doses in clinical trials in Canada and the U.S. We have discussed the high rates of HHE that were observed for all vaccines, acellular and whole cell in the Sweden II trial, which we believe is attributable purely to the study design of that trial.

Of interest, post-marketing surveillance in Canada has shown a decrease of 80 percent in the number of HHE's following the switch in Canada from whole cell based to five-component acellular based combination vaccines.

So in conclusion, both common and serious adverse events with CPDT, whether given as a primary series in infants or as a fourth dose booster, are markedly reduced when compared to whole cell vaccine and are consistent in frequency and nature with those seen with licensed acellular vaccines. And this assessment of the classic formulation of CPDT is further supported by our experience with HCPDT. We conclude that CPDT is safe for use in infants and

toddlers.

Next I would like to show you the efficacy data concerning this vaccine. You have seen this slide already. Just to recapitulate, this is the Sweden I efficacy trial organized by the NIAID as a direct follow-up to the Multi-Center Acellular Trial, and there were four arms. A DT control arm, two acellular vaccines, a two-component and our five-component, and a U.S. licensed whole cell at a nested household contact study.

Here are the primary efficacy results. The five-component acellular vaccine CPDT was shown to be 85 percent efficacious as compared to the DT control arm. In comparison, the two-component acellular vaccine was 59 percent and the whole cell was 48 percent. As Dr. Meade mentioned, this study also evaluated the performance of the vaccines against a case definition consistent with mild disease. The first numbers are against the WHO definition for classic or severe pertussis. Against a definition that would include even the most mild cases, one day of cough, the five-component acellular vaccine was 78 percent efficacious as compared to approximately 40 percent for both the whole cell and the two-component vaccine.

It is of particular interest, I think, that this protection persisted without diminution throughout the entire course of study over nearly two years of follow-up. As you see here, efficacy was maintained for the five-component acellular formulation, in distinct contrast to the whole cell, whose efficacy declined quite rapidly, which explains the high rate of disease of the whole cell receiving group.

Here is another such slide. This slide is intended to show you the uniform performance of the five-component vaccine against differing case definitions of severity of illness. What we have here is duration of cough from one day up to 28 to 30 days. And these definitions are based solely on cough duration, so the numbers here don't exactly match the numbers on the prior slide which included other confirmation. But you see that the efficacy of the five-component acellular vaccine is both high and maintained across the entire spectrum of illness. A perfect vaccine would be one with a perfectly straight line up here at the top of the slide. In comparison, the two-component vaccine and even the whole cell vaccine have got diminished efficacy against mild disease as compared to their efficacy against more

severe disease.

The nested household contact study provides an important look at the vaccine for several reasons. There were analyses that were conducted from those data that we will be showing you, and in addition a household contact study provides an opportunity to see how a vaccine performs in the context of intense exposure. In this household contact study, the five-component CPDT was 75 percent efficacious against the WHO case definition as compared to 42 percent and 29 percent for the two-component and the whole cell respectively. Against a case definition of mild pertussis, the five-component CPDT was 62 percent efficacious against essentially nil efficacy for the acellular and the whole cell vaccines.

The next step was to examine these vaccines further in the Sweden II Trial, where you recall the key differences are that the European whole cell replaced the U.S. whole cell. We need to look at relative rather than absolute efficacy. The majority of the kids were immunized on the standard Swedish schedule of 3, 5 and 12 months.

For the primary case analysis or primary study analysis, efficacy after all three doses

relative to whole cell -- the efficacy for the five-component acellular vaccine was 0.85. In other words, kids were only 85 percent as likely to acquire pertussis if they received the acellular as if they received this known high efficacy whole cell. Although the confidence interval does include one, therefore the whole cell and our acellular did not significantly differ. This is the only study in which an acellular vaccine has been shown to have a point estimate of efficacy superior to that of the European whole cell. The three-component vaccine from Chiron Biocine in Italy had a relative risk of 1.38, meaning it was about 40 to 50 percent higher risk than the five-component vaccine. This is against the WHO case definition. Against a case definition consistent with mild disease, with reference to the whole cell vaccine as one, the five-component vaccine had a relative risk of 1.4, the confidence interval including one. And the three-component vaccine had a relative risk of 2.55, confidence interval does not include one.

DR. FLEMING: Could I just ask a quick question for clarification? The primary analysis in this study was to determine -- was essentially non-inferiority highlighted in yellow where the intention was assess a relative risk of 1.5 against 1, i.e., to

rule out that the five-component vaccine could have a 1.5-fold higher risk than the whole cell. The upper limit is 1.79. So the critical primary analysis of the study did not achieve the objective of ruling out 1.5 relative risk because it is actually 1.79. Am I interpreting that correctly? This is as reported in the Lancet article.

DR. DECKER: Yes, that interpretation is correct. There is the 95 percent --

DR. FLEMING: The most important number in this entire trial is the 1.79 because the hypothesis to be rejected is an upper limit of 1.5. That wasn't achieved. In part it wasn't achieved because there was such under-reporting that the confidence interval was, I am sure, wider than was expected.

DR. DECKER: Yes.

DR. FLEMING: But in fact because of that, this study did not conclusively rule out a 50 percent increase in the rate of cases for the five-component against the whole cell.

DR. DECKER: Yes, that is true. But the point estimate still remains our best estimate of the efficacy. So although we can't rule out the possibility that the vaccine is either 61 percent better than a whole cell or 79 percent worse, our best

estimate is that it is 15 percent better than whole cell.

The second analysis was to look at the efficacy relative not to whole cell but relative to the surprisingly inefficacious two-component vaccine from SmithKline Beecham. The relative risk -- if we take as the standard of one now this two-component vaccine instead of the whole cell, we are actually imposing a more strict test on the candidate vaccine than we would be to compare it to an utterly inefficacious DT control. Compared to this partially efficacious acellular vaccine, the five-component vaccine had a relative risk of .18. Or to put that in terms that are more commonly understood, a relative efficacy of 82 percent compared to this acellular. The whole cell vaccine had a relative efficacy of 87 percent compared to the acellular and the three-component of 60 percent. Against a case definition consistent with mild disease, the relative efficacy of the five-component was 78 percent, 73 percent for the whole cell, and 48 percent for the three-component acellular from the Italian trial.

So in summary, of the three efficacy results we have from the main trial and the household contact trial in Sweden I and from the Sweden II trial

with the hybrid version of the vaccine, we have remarkably consistent point estimates of efficacy that include substantial follow-up periods, ranging from 75 percent in the high intensity household contact study to 85 percent in the Sweden I Trial and 82 percent as compared to a partially effective acellular vaccine in the Sweden II Trial.

To put these numbers in context for an audience accustomed to the U.S. licensed vaccines, from the Sweden I Trial, the efficacy estimate is 85 percent with a tight confidence interval from 81 to 89. Here are the results as reported in the PDR and the patient package inserts for the four U.S. license vaccines. Now I would like to turn the podium back over to Dr. Fahim.

DR. FAHIM: Thank you, Michael. So I am going to be discussing the immunogenicity in U.S. children in support of efficacy of this vaccine. And the way I want to structure this part of the discussion is as follows. I am going to briefly show you one slide on the diphtheria and tetanus response, mainly to complete the data set. I will be discussing with you the use of Sweden II efficacy. We have referred to it several times and I would like to discuss that. Show you evidence in U.S. children

supporting the efficacy of this vaccine. And then finally conclude with a concomitant immunization.

This is the one slide about diphtheria and tetanus. And here without going through every number here, you can see that we have very good responses to both diphtheria and tetanus for short or long term efficacy at the 7 months post 2, 4 and 6 immunization schedule as well as the booster immunization.

Now I would like to just discuss the use of the Sweden II efficacy trial in support of the CPDT efficacy. You heard from Dr. Meade in the introduction about this trial, and he had referred to several comments about it related to the concordance between the serology labs in Sweden II and the U.S. Bridging Trial. The composition of the vaccine was different. The schedule was different. And the efficacy definition was different. And I would like to address each of those.

So for the concordance between the lab, what we have done here is actually at the request of the FDA, we have taken sera, as Dr. Meade explained to you, and we did what we called a serology bridge. Where we took sera from the U.S. efficacy trial and tested it at the same time as the U.S. Bridging sera in the same lab at the same time using similar

technologies. And here is the responses or the concordance for the pertactin antigen. Because this is the antigen you will be discussing a lot today. So here you see here the Aventis Pasteur Canada lab compared to the Swedish lab, and you can see a perfect straight line, a correlation of 95 percent to the log scale and of 98 percent in the linear scale. That tells us that the results from those two labs can be compared to this antigen.

Now here I am highlighting the difference in amounts. The HCPDT had higher amounts of PT and FHA, as again Dr. Meade has explained to you. And to address this point, what we have taken data from Sweden Trial I and Sweden Trial II comparing the schedule that was 2, 4 and 6 in both of those. You may recall that I mentioned in the Sweden Trial II, we had two schedules, a 2, 4 and 6 and a 2, 5 and 12. And in this one here, we are comparing the 2, 4 and 6 schedule between Trial II and Trial I. And you can see for all of the antigens here, with the exception of FHA, the results were very similar. That tells us then that those two vaccine formulations behave similarly in clinical trials with the exception of the FHA. You may recall that the FHA was higher in the HCPDT formulation than it was for the CPDT formulation. We

will be discussing the FHA later on and whether there is any impact on this higher response of the FHA.

Next we talked about the schedule. And, yes, it is true that the schedule was different. For the efficacy, it was a 3, 5 and 12 schedule. But I want to remind you that there was high efficacy, as we will show for the Sweden II only after two doses, and that is what we will be focusing the attention on today.

The relative efficacy was the efficacy criterion for Sweden II instead of the absolute efficacy that was in Trial I. In Trial II, in fact the HCPDT was compared to the two-component as well as the whole cell vaccine. So there were two comparators in there. The HCPDT was shown to be as efficacious as the highly protective whole cell vaccine in this trial. But in addition, the estimated efficacy relative to the two-component provides a more conservative criterion, we believe, than an absolute efficacy to DT control.

Now for the immunogenicity in U.S. children support of efficacy, what I would like to do now is to show you data for the efficacy of the vaccine following a 2, 4 and 6 schedule, so the primary immunization, and provide the efficacy data

for that part or the immunogenicity supporting efficacy for that part. I will then show you data for long-term protection bridging from the third dose to the booster dose and therefore showing immunogenicity data supporting predictive efficacy up to the fourth dose booster. And then finally show the immune response following the fourth dose booster.

So for the first point here, we are talking about immune response supporting efficacy, and here I am going to share with you data for immune response in U.S. and Swedish children. This here is the results of the Serology Bridging Trial Study. Now this is the same data that Dr. Meade shared with you earlier. And you can see for the PT and the FHA and the fimbriae, that is also very similar. Here the pertactin is lower, and that is a comment that Dr. Meade mentioned earlier. You can see here that the results of the pertactin were lower.

This data is now shown here in the reverse cumulative frequency distribution, and you will see these are actually the same reverse cumulative frequency distribution that Dr. Meade has shown. For the PT and the FHA and the fimbriae, there is also a very similar. The quadrant here with the pertactin shows the Swedish efficacy trial here in dotted black

line compared to the U.S. Bridging in green and red. Now Dr. Meade mentioned here that this is qualitatively now and quantitatively different from the bridging trial in the U.S.

Now this raises two important questions. One, why is it different? And second, does it have an impact on the efficacy of the vaccine? So here I am going to share with you some factors that we investigated that may have contributed to the lower response or pertactin response in the U.S. Bridging Trial.

So one of the things that come to mind right away is that the lot that was used in Sweden in 1992 and then used to bridge the U.S. Bridging in 1995, three-and-a-half years later, one can ask the question whether the vaccine has deteriorated over time, this three-and-a-half years. So we will tackle the stability of the vaccine. And then we also investigated the age of first immunization, whether there is difference between the population. And finally, look at the pre-immunization antibody levels.

Now we were actually fortunate that this same lot that I am talking about, Lot CPDT 006, that was used in Sweden I in 1992 and then later on in the U.S. Bridging in 1995, we used this same lot in two

additional clinical trials, one in the U.S. and one in Canada, conducted at the same time as the Sweden efficacy trial in 1992. I would like to draw your attention here to the results. As you see here, the North American Trial, the two in the U.S. and the one in Canada, the results are reasonably similar and lower than the results shown in Sweden. So one can conclude from that that the stability was maintained or the stability was good over that period of time, and it would not be the reason that we see lower responses of pertactin in the U.S. Bridging Trial.

We then looked at the age of first immunization. And here on the left panel, you can see the age distribution at first immunization between Sweden I and the U.S. Bridging Trial. Suffice to say that there is a difference between the age of first immunization in those two populations.

We then looked at the pre-immunization levels, whether that has played or was a factor in that lower immune response. And for that, we stratified the data based on the pre-immunization levels, and we divided into three categories. Below 3 ELISA units, between 3 and 10 ELISA units and above 10 ELISA units. And the way we constructed this is we here on the left panel here, we see the pre-

immunization for one of the children in this category. So this is one child. And we constructed similar lines for each of them. And on the right panel, we see the post-immunization. So this child here had a 1.5 pre-immunization levels and reached 160. Now the steepness of the curve tells you the immune response achieved. We then populated using this same -- a group of children here, we populated this graph here. And for ease of interpretation, we actually took the average then. And now we took the average and compared Sweden I with the U.S. Bridging Trial. You can see that for the children who had similar pre-immune levels, they had similar slopes of antibody response and achieved similar responses post-immunization.

At the other extreme of the spectrum, when the pre-immunization levels were much higher, now you see that the shape of the curve changed and now it is shallower, indicating there is an inverse relationship between the pre-immunization levels and the post-immunization levels. One additional observation here, you will see that in the U.S. Bridging Trial, there were more children with higher pre-immunization levels than were in Sweden. So this now tells us that maybe there is a correlation between the high pre-immunization levels in the U.S. Bridging and the post-

immunization levels for the pertactin responses. As expected, the population in the middle between 3 and 10 ELISA units gave slopes that are intermediate between those two extremes.

To conclude those factors that we investigated, we showed that the clinical evidence indicated that the stability of the vaccine over three years was maintained. Similar immune responses were achieved in the U.S. and Swedish children when pre-immunization levels were similar. And the U.S. Bridging Study had more children with high pre-immunization levels than did Sweden I. This may have contributed to the difference in immune responses. I would like to also indicate that this is not unique to the CPDT and it has been shown with other vaccines. Here is data from the Biocine's CLAVO-3 component and the SKB Infanrix licensed vaccine for pre and post. I would like to draw your attention here to this column showing MAPT -- these are U.S. children here compared to the Italian clinical efficacy trial, for either the Biocine's CLAVO or the SKB Infanrix there is a reduction in response to pertactin. And if you now look at the pre-immunization levels here, you see that the pre-immunization levels were higher in U.S. children than in the Italian population as well.

Now that is all good and well. These are maybe factors that may have contributed to the lower immune response. Do they matter? Do they have an influence on the efficacy of the vaccine? I would like to tackle that now and show you evidence that the pertactin response in U.S. children supports the efficacy of the vaccine.

For that I would like to compare the pertactin response in the U.S. and the Swedish population and share data with that, and also look now at the redundancy and synergy of the protective antigens. As I mentioned earlier, one of the characteristics of this vaccine is that it has multiple protective antigens in its composition.

I showed you these graphs before. These are reverse cumulative frequency distributions comparing the Swedish efficacy trial in dotted black with the green and red for the U.S. Bridging Trial. And again common to them the pertactin response here. We were actually very fortunate to have two efficacy trials as I indicated earlier. One of them in Sweden Trial II that used the HCPDT vaccine that showed high efficacy of the vaccine had an efficacy estimate between doses 2 and 3 that allowed us then to look at that. Now when we take the data after dose 2 -- the

immune response data after dose 2 -- from that trial and now construct similar reverse cumulative frequency distribution for that population, this is what we get. In blue here is the reverse cumulative frequency distribution of the Swedish population after two doses. One will notice here that the responses for the pertactin in the U.S. Bridging is bracketed between two efficacy trials showing high efficacy of our vaccine, indicating then that the U.S. Bridging immune response here would afford protection to children because it is bracketed between those two efficacy trials with high efficacy of the vaccine.

This is the geometric mean titers that I just showed you on the reverse cumulative frequency distribution showing the responses to PT, FHA, fimbriae and pertactin. And Sweden II the same thing. And again, to indicate that the results of PT, fimbriae and FHA were comparable to Sweden I, and there is also pertactin well bracketed between Sweden I and Sweden II.

Now to focus the attention on this pertactin response here. This is Sweden I showing 85 percent efficacy of the vaccine. Sweden II showing 82 percent efficacy of the vaccine. And these are the results of the pertactin here. And this is the U.S.

Bridging Trial bracketed in-between.

So these are the conclusions from those studies. The immune response to PT, FHA and fimbriae are comparable in Sweden I and the U.S. Bridging Trial. The immune response to pertactin in the U.S. Bridging Trial Study falls qualitatively and quantitatively between Sweden I and Sweden II after two doses at the 3, 5 and 12 schedule.

This observation was actually seen also for another licensed vaccine in the U.S. This is from the Infanrix Italian study at a 2, 4 and 6 schedule showing this response post-vaccination. This is the same vaccine studied in Germany showing this response with a different schedule, a 2, 3 and 4 schedule. And this is the MAPT study with the U.S. population showing an intermediate result.

Now I would like to turn over to look at the redundancy and protective antigens providing synergistic effect of the vaccine. And for that I would like to draw data from the Sweden I household contact study. Now we heard about this several times today. And for construction of this table, what the investigators have done is that they stratified the pre-exposure antibody levels of the population in the household contact and from that constructed data to

show -- from regression analysis data to show that a level of 5 ELISA units for each of PT, fimbriae and pertactin reduces the risk of pertussis. In addition, they also noticed that levels above 5 does not enhance protection any further. They also noticed that for the pertactin or fimbriae, a level above 5 provides good protection against pertussis. When the level of pertactin and fimbriae are both above 5 ELISA units, we have even higher protection here. When these two antigens are not above 5 but the pertussis itself is above 5, we have intermediate protection.

Similar observations were shown also for mild disease. Now the table I showed you before is for WHO definition or typical disease. This is for mild disease. And here you see similar observations, but it shows also more importance here for pertactin and fimbriae in the mild disease as compared here for the vaccine efficacy of that.

Now I would like to mention one comment here. This is not vaccine-specific. This is the total population in that household contact.

The importance of pertactin and fimbriae was also noticed in Sweden II. Here we are showing the results of Sweden II after two immunizations and showing the high efficacy of the whole cell vaccine

and the HCPDT five-component vaccine here, relative efficacy. And you will notice here the responses to fimbriae and pertactin in both of those vaccines. Even with the lower response to PT, we have this high efficacy compared to the three-component where you have high pertussis toxoid response here and higher pertactin but no fimbriae and the relative efficacy was lower.

I'd like to draw your attention here to the U.S. Bridging, and you see that the results here, as stated earlier, were higher than the Sweden II HCPDT after two doses.

Now this now shows maybe that we have the efficacy after three doses. But is this efficacy -- will this efficacy be maintained up to the booster immunization? For that we draw data from long-term protection as well as antibody decay. This is a slide that you have seen earlier from Dr. Decker showing the persistence of the protection for the CPDT vaccine. We actually extended this per the technical report of the principle investigators up to the end of the follow-up period. Here it shows that throughout this follow-up period, the CPDT maintained high efficacy against pertussis.

This now also allowed us -- or allowed the

investigators to construct antibody decay rates by taking sera samples at various periods of time during this follow-up period. So after one month following the 2, 4 and 6 immunization, this was the level of antibody response to each of the antigens. At 13 months, we show a lower level of responses to the antigens. And towards the end of the follow-up period, we have here quite a dramatic decline of the antibody response. However, even with this decline, as I mentioned earlier, the efficacy was maintained up to that point.

This allowed the investigators now to look at antibody decay rates and we calculated from that antibody decay rates here for each of the antigens. Now in order to validate this antibody decay rate, what we have done for the U.S. Bridging Trial is made an estimate from the antibody following the 2, 4 and 6 schedule and estimated now what the levels would be up to the booster immunization in the U.S. schedule. This is then the estimated pre-booster levels. We then looked at the actual assay, the actual test data from the sera pre-booster, and these were the levels. We can see that reasonable similarity between the two levels were achieved, telling us that these decay rates may be used to estimate levels of antibody at a

certain period of time.

We used those decay rates to estimate in Sweden II what the levels would be prior to the third dose at 12 months of age. Now I would like to remind you in Sweden II, they did not take antibody pre the third dose. So we estimated that here and these would be the antibodies estimated from the antibody decay rates. And this slide also is showing for Sweden I household contact pre-exposure antibody levels, and you can see here these are them for PT, FHA, fimbriae and pertactin. We also show here Sweden I at 23 months after the third dose. These are the antibody levels that maintained efficacy throughout the follow-up period.

I now draw your attention to this right-hand column for the U.S. Bridging. These are the assay levels pre-booster. You can see that for each of the antigens in the U.S. Bridging, the levels of antibody were similar to three efficacy trials showing high efficacy of the vaccine up to the booster immunization in the U.S. Bridging Trial.

And then finally I would like to show you immune response following the fourth dose booster. For this we will draw data from four trials, phase II, IIB, IIC in Canada, and the NIAID Cycle I. I will

actually only show you data from the phase II trial, because it had the larger number of kids. But you will actually have in your handouts the data from the other three trials.

In here, this is just the one table I would like to show. These are the pre-booster levels for each of the antigens and these are the post-booster levels. And for each of the antigens, you can see a significant boosting effect showing that these kids were primed for all of these antigens and responded with significant responses. Here these are the fold increases. All of these responses were higher than in Sweden I after three doses.

To summarize then this part of the discussion, we show the immune responses that support efficacy following three primary doses. The U.S. Bridging Study results fall between Sweden I and Sweden II after two doses. The presence of antibodies to PT, fimbriae or pertactin alone or in combination reduces the risk of typical and mild disease. Either fimbriae or pertactin provides sufficient protection against typical disease. This is data from the household contact. And both fimbriae and pertactin provide synergy against mild disease. The CPDT vaccine provides sufficient immune response to all of the

antigens, including pertactin, to afford protection in U.S. children.

We also showed data to show that the antibody levels prior to the fourth dose booster provides sufficient protection against pertussis, therefore comparable efficacy to the trials in Sweden would be expected. Significant booster responses are seen across studies indicating priming and long-term protection.

And finally in this part of the protection, I would like to show concomitant immunization data. This is an overall experience for the concomitant immunization with the CPDT vaccine for the infant series. This here is safety data with IPV and Hib, Hib/IPV and hepatitis B. And this is the data base we drew the safety from. We also have data with the HCPDT formulation at 2, 4 and 6 months of age as well as the 3, 5 and 12 schedule. And again with IPV and Hib, or Hib/IPV combined, and again showing a large safety data base.

For the fourth dose booster, we have data with CPDT or HCPDT with the IPV or Hib, again showing a large data base with a concomitant immunization at the fourth dose booster.

For the immune response, here we are

showing concomitant vaccination in the U.S. Bridging Trial with Hib, polio and hepatitis B. And here we are showing with at least one vaccine concomitant or all vaccines concomitant. And without going through all these results, we can see that these are the expected results for a good vaccine.

For the fourth dose booster, we have data here from the CPDT with PRP-T as well as HCPDT with PRP-T. These are concomitant injection. We also did separate injections 30 days apart. And you can see that we have very good responses following the fourth dose booster with good seroconversion rates.

For the polio type I, II and III at the fourth dose booster with the HCPDT vaccine for IPV and OPV, again you see geometric mean titers that are respectable with good conversion rates -- seroconversion rates.

This is the summary of concomitant immunization. And maybe I will just skip over to the overall conclusion that will include conclusions for the concomitant immunizations in any case.

For the conclusions then, we have shown you the composition of this vaccine with multiple protective antigens -- PT, FHA, pertactin and fimbriae 2 and 3. This is the slide that Dr. Decker showed

earlier for the efficacy of this vaccine showing high efficacy of the vaccine maintained for mild disease as well as moderately high disease. This shows us that this vaccine is protective for even mild disease, which is important from a public health point of view.

The FDA has asked three questions related to efficacy, safety and concomitant immunizations, and I would like to conclude with remarks related to each one of those.

So for the efficacy, we have convincing efficacy data from the Swedish Trial, both Sweden I and II. We draw data from immunogenicity for the U.S. and Swedish Trials, and we showed antibody decay data all supporting efficacy in U.S. children after 2, 4 and 6 months primary series and until the booster dose.

We have shown you data from multiple studies in Swedish and U.S. children showing the rates of common side reactions as well as serious and adverse events that are markedly lower for the CPDT vaccine than for the whole cell vaccines. In addition, we also showed you comparable data with acellular pertussis vaccines licensed in the U.S. for both the primary series as well as the booster dose.

And finally, for concomitant immunization

Mahery, et cetera, to assure inclusion of the inner city population?

DR. DECKER: The -- that is a great question. The Mahery and Vanderbilt have had a fairly strong tradition of collaboration, which has strengthened over the last decade. That infrastructure was not in place at the time this trial was designed. And so unfortunately we didn't have the opportunity to work with our Mahery colleagues on this study. On the other hand, because the study was multi-center and nationwide, there was good representation of minority groups. For example, as you probably know from your reference to Mahery, we have a substantial proportion of blacks in the national enrollment and a large proportion of Hispanics from Baylor and so on. And in the overall trial publication, there were about a dozen papers published as a supplement to Pediatrics that I think you have. And if I remember correctly, one of those papers actually focused on the question of racial differences, if any, among the responses and the data there were reassuring.

DR. FAGGETT: A follow-up. The question of under-reporting, we as inner city physicians -- and patient resistive. So you are seeing improvement in that now? Is that what you are saying?

DR. DECKER: I am sorry, I didn't understand your question.

DR. FAGGETT: The question of under-reporting was addressed as well?

DR. GRIFFIN: Under-reporting for what? Adverse events?

DR. FAGGETT: Correct.

DR. DECKER: Well, these -- you know these were solicited adverse events with close follow-up. So I don't think that -- even if differential under-reporting is a public health problem, I don't think it is a problem in the context of a specific study like this.

DR. GRIFFIN: Okay. Ms. Fisher?

MS. FISHER: In the Swedish trials comparing whole cell and acellular pertussis vaccines, including this product, there were certain excluding health conditions which prevented certain children from being included in the study. I understand from the information we were given that children were not included in the study if they had serious chronic illness, including failure to thrive, progressive neurological disease and uncontrolled epilepsy. Children were withdrawn from the study if a previous dose was followed by a seizure with or without fever,

persistent crying, cyanosis, fever of 40 degree Centigrade, hypotonic hyper-responsive episode and allergic reactions. If those children were excluded from this study, am I to understand that this product has not been tested for safety when given to those categories of children which in fact are the very children in the United States who routinely get vaccinated, including premature babies who are failing to thrive and sick children and children who after vaccinations suffer persistent crying, convulsions with or without fever, fevers of over 40 degrees Centigrade, hypotonic hyper-responsive episodes and other kinds of reactions?

DR. DECKER: Well, as you know, the larger question that you are asking has been a subject of considerable debate for a while. And that is who should be included in trials of pharmaceutical products. For example, it has long been routine to exclude women from trials and people question whether that is appropriate. The exclusion is based in a laudable motive to avoid any chance of injuring the fetus, but then it denies you the data you need to evaluate that. These trials were designed in accordance with what were the accepted standards at the time, and the accepted standard was to include

only children that appeared to be normal and healthy. If there was any question, they were excluded. You know, it is a very worthwhile question whether studies should incorporate those, but it is a difficult question and it is not one that we can answer in the context of this study.

MS. FISHER: The reason I am asking the question is that when this vaccine is licensed, I think it is very important for it to be clearly understood that the categories of children who were excluded from the study have not been -- that this product has not been judged to be safe to be given to the children who were not included in the study. And that, of course, is a policy decision, but I think often it is not recognized at the time of licensure.

DR. DECKER: Well, as I said, this is an important question. But I think we have to recognize it as a broader question than this one vaccine. Your comment is equally applicable to every other acellular pertussis vaccine in the United States, and we are going to have to look to larger answers to these larger questions. With respect to this vaccine, we are all going to rely on the recommending bodies as we do with the other vaccines.

DR. GEBER: Could I just make a comment?

Ms. Fisher is quite correct that many of those conditions --

DR. DECKER: I am sorry, I can't hear you.

DR. GEBER: Ms. Fisher is quite correct that many of those conditions led to exclusion. But just for the record, prematurity was not an exclusion for either of the Swedish efficacy trials.

MS. FISHER: Yes, I was specifically talking about prematurity failure to thrive.

DR. GRIFFIN: Okay. Dr. Stephens?

DR. STEPHENS: We are being asked to comment today on the classic formulation of this vaccine. A lot of the data, especially in the Sweden II trial, has to do with the hybrid formulation. Can you kind of comment on your feelings about those combined data sets and reassure us, if you will, that they are comparable vaccines?

DR. DECKER: The -- as I mentioned, the two formulations were designed -- the reason there were two formulations was that after the classic formulation was designed, it was intended to include the minimal level of each antigen necessary to produce a protective antibody response. And then some data became available from other studies of other products early in the decade suggesting interference between

acellular pertussis vaccines and other vaccines. So in order to be prepared to move forward with a combination vaccine that would escape that problem, the hybrid formulation was developed with augmented concentrations of some of the key antigens. Now as you have seen from the antibody data we have shown, the subsequent experience has shown that there is less difference in the antibody response to the two than you might expect. In fact, they are quite comparable. So we think that given the small difference in the vaccines compositions, the antibody data showing comparability -- the very uniform efficacy data -- that these data can logically -- the HCPDT data can logically be used in support of the CPDT application. Clearly with respect to safety, the data ought to be fully useful because it is not reasonable to think that a vaccine with somewhat more antigen in it is going to lead to misleadingly lower reactions. With respect to efficacy, I think we have to look at the antibody responses, which are really very similar. Raafat, do you want to do --

DR. FAHIM: You captured everything I would have said. In essence --

DR. GRIFFIN: Use the microphone, please.

DR. FAHIM: Sorry. The responses were

similar, as I have shown in the slides showing the responses being similar. The only antigen that was different was the FHA. And we have seen from those efficacy trials that the FHA antigens -- particularly for this formulation in these settings -- was not a significant contributor to protection.

DR. DECKER: It was something that wasn't known at the time the design decisions were made, but it has been shown both by the household contact study and by the German researchers, Jim Cherry's group, analyzing the follow-up data from their study. It is that FHA surprisingly appears to be of low importance in the context of vaccines that contain the other components.

DR. STEPHENS: Just a quick follow-up question. The amount of pertactin in this vaccine as compared to other vaccines, how was that choice made? Pertactin?

DR. FAHIM: The choice of pertactin was actually made based on animal immunogenicity studies at the beginning during the development of the vaccine. As you can imagine, during the development one would estimate the amount that you want to put in each vaccine based on the animal immunogenicity studies. And we put that based on those studies.

DR. GRIFFIN: We have Diaz, Katz and Kohl and then a whole bunch of people on this side.

DR. DIAZ: If in fact the two formulations are similar, you brought up some interesting discrepancies in the HHE adverse events that were seen with the Sweden II trial compared to the Sweden I. And explanations that were put forth were along the lines of over-reporting. And there was some supporting evidence in comparison with the Italian trial that you presented that showed less HHE in the Italian trial and yet more when that vaccine was used in Sweden II. I guess I question the opposite and perhaps wondering if in Sweden I there was under-reporting per se by virtue of not having a definition to work with to document HHE. And if you could compare with me or provide information about the Italian trial and some of the follow-up Canadian and U.S. studies if in fact a similar definition as the Sweden II trial was used in those studies or if they also perhaps could have been a factor of under-reporting in those studies.

DR. DECKER: Well, let me tackle one aspect of it, because that is a very interesting question and perhaps Dr. Fahim can tackle the other part of it. Under-reporting or over-reporting. Yes, both are probably true. It all depends upon your

perspective. Particularly when you are dealing with a relatively subjective phenomenon like HHE. The characteristics of the definition used, and in particular the way you instruct the researchers is going to have a profound effect on how much you collect. So from the point of view of the Sweden II Trial, every other study ever done has under-reported HHE. From the point of view of all the other studies, Sweden II over-reported. Which is the true view? You could argue endlessly about that. But the potency of even a minor change was in fact shown to you on those fever curves, where between the phase II and the phase IIC studies, the change of two-tenths of a degree in the lower limit of fever doubled or tripled the number of kids that were included. And that is for an objective measure like fever. So it is quite clear that for a more subjective measure like HHE, differences in the definition can have a profound effect.

Now as far as evaluating the safety of this vaccine we bring you today, I think the key question not is which is the right definition, but how does this vaccine -- what is the safety of this vaccine in the context of our experience with other vaccines. So the important point I was trying to make

with the Sweden II trial is not necessarily that they were right or they were wrong in their definition, but simply they were different. And we saw that all four vaccines evaluated in Sweden II had a uniformly elevated rate of HHE compared to the same vaccines performance in other trials. Because the body of experience of the people in this room is built largely on the more numerous other trials that use the definition that produced lower rates of HHE. Our concern was that people would look at the rates from Sweden II for our vaccine and say, why, it has got more HHE. And that is not the case. It is not that this vaccine has more HHE. It is that that study definition detected more HHE for all the vaccines in that study. So I want to separate those issues very clearly, because it is a worthwhile question whether perhaps all studies should use the Sweden II definition. But that is a question distinct from the question of whether this vaccine is safe for American children.

DR. DIAZ: And just a quick follow-up. I may have missed it. In your comparison of your antibody responses between Sweden I and Sweden II, which assays were used? Were they the latter assays, the validated assays or the prior?

DR. FAHIM: These two assays -- or actually the results that you have seen here are actually done in Sweden. Both of them were done in Sweden. So these are the Swedish assays in the same lab.

DR. GRIFFIN: Okay. Dr. Katz?

DR. KATZ: I was very interested in your data on the concomitant or the separate injections. In both of your studies, it seemed that there was an advantage to the anti-PRP titers. The geometric means were twice as high or greater if you gave them concomitantly rather than separately 30 days apart. How do you interpret that?

DR. FAHIM: Maybe it helps. We looked at it and I didn't want to comment on it because it is very difficult to interpret. But these are observations that we made.

DR. KATZ: I think they are important.

DR. FAHIM: I think so too.

DR. GRIFFIN: Okay, Kohl and then Hewlett and then Huang.

DR. KOHL: There is a recent interesting paper by Dr. Reynolds, who I believe is in the audience, looking at whole limb swelling after the acellular vaccine. And in that paper, she was able to

associate the degree of whole limb swelling with increasing levels of diphtheria toxoid primarily. This current vaccine that you are putting forth has considerably more diphtheria toxoid than Tripedia, which is your presently licensed vaccine. And I was wondering if you specifically looked at whole cell swelling in the populations that you looked for side effects?

DR. DECKER: Dr. Fahim may have to augment or correct part of my answer. But my memory is that the observation of this whole limb swelling is more contemporaneous than these studies and therefore that wasn't a specific -- since those observations have been made, every study looks for that. Prior to their first being made, nobody thought to look for that. So I don't think we have specific data on that question from our earlier studies. But in Dr. Reynolds paper, she looks at three adverse reactions -- swelling greater than 50 mm, whole limb swelling, and if Peggy is here she can help me. There is a third one she looked at. What was the third one?

DR. GRIFFIN: Identify yourself, please.

DR. REYNOLDS: (Off microphone) Margaret Reynolds, University (inaudible). I looked at the entire upper -- I looked at entire thigh swelling

post-dose four, entire upper arm swelling post-dose four, and also the percentage of children with greater than 5 cm of swelling.

DR. DECKER: Thanks, Peggy. And a number of vaccines exhibited at least some children with that. The vaccine we bring you today was among those. But the incidence rate of this phenomenon for this vaccine was lower than for other -- some of the other U.S. licensed vaccines. It fell -- as with the other adverse reactions we showed you, it fell more or less in the middle of the pack.

DR. GRIFFIN: Okay. Dr. Hewlett?

DR. HEWLETT: I would like to follow up on Dr. Stephens' question about the relationship between the two vaccines without probing into company long-term strategic planning. I am trying to understand the decision process in this vaccine. I think it was inferred at least somewhere in the written material that the hybrid vaccine was for the purpose of combined -- incorporation into combined vaccines, and the classical one not. Are there countries in which the hybrid vaccine alone is licensed and being used at the present time and/or the classical vaccine?

DR. FAHIM: We have licensed, as Ms. Minchella showed you, in 23 countries the CPDT vaccine

for which we are seeking license. There is only one country in the world where the HCPDT is used and not in combination. That is I think Taiwan or Hong Kong. And that is because the licensing process is like that. But we don't -- we are not licensing the HCPDT alone for any of those countries, only in combinations.

DR. DECKER: And let me point out that we don't particularly support using it alone because there is no benefit. You've got essentially equal efficacy from the classic, which includes less antigen, and one of the design philosophies here was to use the minimum amount of antigen consistent with efficacy. That was how it was designed.

DR. GRIFFIN: Dr. Huang?

DR. HUANG: Dr. Fahim, you have us a great deal of data in a short time, and you may have given the answer to the question I am going to ask. But because we are focused on the use of surrogate immune markers for efficacy in the United States, I would like to just probe this whole area a little deeper. You gave an interesting possible explanation for why there is a difference in the immune response in U.S. children versus Swedish children in relation to pertactin by saying that the pre-immune levels of

these children were higher than for the Swedish children. Did you also measure the pre-immune levels for the other antigens and did they also -- were they also higher? And also after multiple doses, did they decline? I mean, they weren't lower later as we know.

DR. FAHIM: That is a very good question. Actually, we did obviously look at the pre-immunization level, and I showed one slide with that. And if my memory serves correctly, there is only the pertactin was the one with the highest pre-immunization level in the U.S. versus the Swedish. It was the only antigen that had higher levels in the U.S. versus Sweden. Does that answer your question?

DR. HUANG: Yes, it does.

DR. FAHIM: Thank you.

DR. HUANG: Of course that leads to the other question of why.

DR. FAHIM: Dr. Decker is adding that it may be cross-reactive antigens with other things.

DR. FAGGETT: One more question. The fact that the Swedish kids -- well, they didn't have pertussis -- 1979 was when they stopped it, right? So was that period from 1979 until the present study, was there an effect there as well? Did that have an effect on the study, the fact that there was no pertussis in

Sweden during that time?

DR. FAHIM: It could very well be that the Swedish population was not immunized and therefore the disease may be shifting to lower infants than in adults. I don't think it is a unique observation for countries that don't immunize against pertussis. Dr. Decker, do you want to add?

DR. GRIFFIN: Dr. Goldberg?

DR. GOLDBERG: A comment on the Swedish II Trial.

DR. GRIFFIN: Speak into your microphone, please.

DR. GOLDBERG: Sorry. On the Swedish II Trial, you switched control groups because the -- that is the -- the DTaP3 was doing more poorly. I am sorry, DTaP2 had a much poorer efficacy than your purported control. It could just be that it was doing harm in that study. So I think that basically -- that analysis really adds nothing and in fact detracts from the main focus of your presentation and your message. I mean, what it does is improve the look of the HCPDT and the DTaP3, but it really is an irrelevant analysis and could be potentially misleading in this context.

DR. DECKER: I am sorry, I disagree. I think it is neither irrelevant nor misleading, but I

think I must have failed to explain it well. Let me take one more quick shot at it. First of all, we didn't switch control groups. The --

DR. GOLDBERG: It is a secondary analysis. I recognize that.

DR. DECKER: Once it was -- there was a conflict right from the beginning because there was simultaneously the desire to have a placebo or an inactive control group to be able to calculate absolute efficacy and a desire to offer all the children pertussis vaccine. The decision to offer all the children pertussis vaccine won out. And, therefore, there was no inactive arm. But once it was recognized half or two-thirds of the way through the trial that the two-component vaccine was of low efficacy, it was recognized that an analysis could be made using a comparison to that vaccine's performance as a pseudo-placebo. Now in a comparison to a true placebo, you have a large number of cases in the placebo group because they didn't receive an active agent. And you are comparing that large number against a small number in your vaccine group under investigation. Here, the number of cases in this pseudo-placebo arm is not as large as it would have been had it been a true placebo. It is a reduced

number of cases. So a comparison to that is actually a harsher comparison than against a true placebo.

DR. GOLDBERG: I guess we can agree to disagree on this. However, from the perspective of your planning -- and this follows on the question that Dr. Fleming asked you earlier about the -- how you designed the trial and whether it was really for equivalence or for detecting an improvement. And it seems to me that what this does is essentially make everything look fine relative to something that is worse than what you thought was a reasonable control. This is a problem that plagues all active control trials. However, very often what can happen is that what you think is an active drug could be doing harm in a specific context. So I am just pointing this out.

DR. DECKER: I think your comment is well applicable to a pharmaceutical trial. But here for a vaccine, I think it is unlikely that given the two-component vaccine actually induced pertussis. So I don't think it caused harm.

DR. GRIFFIN: Dr. Fleming?

DR. FLEMING: I would like to follow up on some related issues focusing on the interpretation of the Sweden II Trial, which the way you presented your arguments is really pretty critical. Because you are

in essence recognizing that the U.S. Bridging studies are falling in-between Sweden I and Sweden II, and hence one has to argue that there is convincing evidence of efficacy in Sweden I to close this argument. Let me lead into my comments, though, by saying there are two fundamental questions on efficacy that I hope this panel sometime over the next six hours is going to address. Because for me to answer the efficacy question, I have to know the answer to this. The first is what is an adequate level of efficacy for CPDT? The only answer that I have gotten so far on that is from the planners of Sweden II who said it is unacceptable for the relative rates to be 50 percent higher in the CPDT vaccine compared to the whole cell vaccine.

The second fundamental question is once we have that nailed down, what is the antibody response that is needed to ensure that we can reliably conclude that we have achieved that level of efficacy? Let me leave these two questions for what I hope will be extensive discussion, because it seems to me we have to understand the answers to these in order to be able to answer the FDA's first question.

Let me comment specifically though on this fundamental argument of what we do know from Sweden I

and Sweden II and the consistency the sponsor has presented that these results in Sweden I and Sweden II are very consistent. That is a bit perplexing to me because as I look at Sweden I and Sweden II, the one thing that is in both studies is the whole cell against the vaccine of interest, and I realize here I am allowing you to do what you are suggesting, which is to consider these two vaccines, your two products, essentially as comparable. So I will go with that assumption at this point. In the Sweden I Trial, the relative efficacy of the CPDT against whole cell is 71 percent. The relative efficacy in Sweden II, i.e., the relative risk is .85, is 15 percent. So there seems to be an interesting discrepancy there that I would like to understand if I am going to try to conclude that these two are consistent.

The second issue that bothers me about Sweden I versus Sweden II is Sweden I is active surveillance. And as was recognized in the discussion of the Sweden II article, it was looking at around an 8 percent per year incidence. Even if you adjust for, as the Sweden II article indicated, a reduction in the rate of pertussis over those two years in Sweden, it doesn't begin to account for the striking reduction in the actual passive surveillance identification of

cases, which is anywhere from 10 to 100-fold less frequently detected in Sweden II compared to Sweden I. So one is left with some very interesting observations. In Sweden I, 95 percent of the cases that were detected were detected after the third dose. In Sweden II, 25 percent of the cases that were detected were detected after the third dose. Dr. Decker drew my attention to the point estimate when I pointed out that Sweden II did not meet its primary hypothesis, as Dr. Goldberg is pointing out, which is a comparison against whole cell ruling out a 50 percent increase. Because that relative risk, I think, was 1.79. But Dr. Decker said, but look at the point estimate. It is .85. Well, that is true. There were two fewer cases, 13 versus 15. But that is only looking at the cases that occurred after the third dose. It is reassuring that the point estimate is favorable, but an under-powered trial with a positive point estimate is inconclusive to the question that the study was designed to address. What bothers me even more is if we look at all the cases after the first dose, there is actually an excess of cases. So if you draw me to the point estimate, I will look at the point estimate. The point estimate is 1.25 after the first dose. It is not less than one, it is greater

than one. And I realize the argument that is often given. We are going to look after the third dose because that is where the greatest sensitivity is. But it doesn't mean that cases that occur after the first dose aren't just as real to the children that have those cases. When you look at the randomization, there are more cases that are occurring after the first dose on the acellular pertussis vaccine than on the whole cell vaccine.

I am also greatly troubled here by this under-reporting. Because if 75 percent of the cases are occurring after the first dose, clearly that means that where you are putting so much of your emphasis is over a period of time where there is dramatic under-reporting, only 28 total cases. But interestingly, you have drawn our attention to the data after the second dose. You have drawn our attention to that because you were trying to get at the serological comparisons. But if you in fact look at what happens after the second dose before the third dose, there is an excess of cases on the acellular pertussis vaccine over the whole cell. I come back to the question to the committee. What is it we are trying to determine here? That there is any efficacy, or are we trying to rule out that there is more than a 50 percent increase in