efficacy. Our point estimate is that there is a 50 percent increase in efficacy over the region that your secondary analysis was drawing our attention to, which was the period between the second dose and the third dose. So I think there is an awful lot of confusion for me, if I am trying to scientifically, objectively interpret the data from Sweden II. My view of Sweden II is that the passive surveillance didn't really work to be able to detect pertussis cases. It will work to detect those events that are so profound that with passive surveillance they will be reported. So it is a great study for studying rare safety concerns. I have serious concerns interpreting it, though, when I am trying to get efficacy for the pertussis cases when they are so grossly under-reported, especially after the third dose.

DR. DECKER: Dr. Fleming, you raised so many points that my memory is overwhelmed. So if I don't address them all, forgive me. But let me pick the ones that were most striking to me. First off, I regret that I wasn't sufficiently clear about the key difference in the whole cell control groups in these two studies. Sweden I used a United States whole cell vaccine that was proven to be only 36 to 48 percent efficacious. Sweden II used a European whole cell

vaccine and the studies in the literature of that vaccine suggest 80 to 90 percent efficacy. So the fact that the performance of the acellular against this dramatically shifting whole cell benchmark differs is not surprising and is hardly an indictment of the acellular.

DR. FLEMING: By the way, just to interrupt, a valid point. And it gets at trying to explain why there may be these inconsistencies in the first study and the second study. It doesn't in any way, though, address the issue of what the intention was, which was to rule out a 50 percent increase in the risk of pertussis cases against the more effective whole cell vaccine used in Sweden II.

DR. DECKER: The second issue of importance is your observation that with respect to the European whole cell vaccine, there was an excess of cases in the five-component acellular group after the first dose. After the second dose, rough comparability. Is that fair?

DR. FLEMING: No, it was also higher.

DR. DECKER: Also higher?

DR. FLEMING: As you showed us the information between the second and third dose -- I wanted to jump up, but I didn't want to interrupt your

flow. You were using that data to get at serologic information, but it actually points out that between the second and third dose, there are more cases in your vaccine than on the whole cell.

DR. DECKER: You have the numbers in front of you and I am going by memory, so forgive me. But is it --

DR. FLEMING: .13 versus .18 as I recall.

DR. DECKER: Okay. And then it was .85 after the third dose. I am absolutely comfortable bringing this vaccine to this committee based on any of those numbers because I want to remind you that every acellular vaccine already licensed in the United States was less efficacious than the whole cell control vaccine in the study that they were licensed on with one exception, and that would be the one vaccine that was evaluated in the Italian trial which used that inefficacious U.S. whole cell vaccine. The other three were compared to European whole cell vaccines and had lower efficacy. So this is not remarkable. What is actually of interest is that for at least the study design assessment of efficacy after three doses, we have got a point estimate that is superior to the European whole cell, and that has never been observed before. I believe the totality of

the data support the --

DR. FLEMING: You are saying the post-third dose?

DR. DECKER: Yes, right.

DR. FLEMING: That we have 15 cases versus 13 cases in 40,000 children? That is the impressive take-home message?

DR. DECKER: No. The impressive take-home message is that the efficacy of this vaccine compared to a European whole cell is very similar.

DR. FLEMING: 15 cases versus 13 cases after the third dose in 40,000 children. That is the data, is that correct?

DR. DECKER: That wasn't the end of my sentence. I was going to say after the first dose you said that there was a -- if I am remembering your numbers right, and I don't have them in front of me. I am not trying to misquote them.

DR. FLEMING: It is 58/48 after the first dose.

DR. DECKER: 58/48. That is at least as good as was reported for other U.S. licensed acellular vaccines that were compared to European whole cells. We need to -- I think it important that we not apply a different set of standards today than we have

applied on all other such occasions. This vaccine very comfortably fits in the spectrum of U.S. license acellular vaccines, and indeed I believe is more efficacious than other U.S. license acellular vaccines. It is true that in Sweden II, the vaccine was subjected to a tough standard, but that shouldn't be held against it.

DR. FLEMING: The first question that I raise to the committee is what is the standard we should hold. So I am agreeing with you that it is something -- that it is a question that is worthy of discussion. What I am trying to probe at this point, though, is the confidence that you are deriving from Sweden II in terms of the efficacy message for your vaccine against the whole cell, particularly relative to the post-dose three comparison, where it seems to me that there is such dramatic under-reporting that it is extraordinarily difficult to make any conclusion, and certainly the hypothesis that generated this study was not met. The non-inferiority hypothesis was not met. I agree with you, that doesn't lead me to believe that we conclude inferiority, but rather that there is such dramatic under-reporting, that this study is so dramatically under-powered that one is really hard-pressed to draw any conclusion about relative

efficacy, particularly using only the post-third dose data.

DR. DECKER: All right. You raised two important issues there and let me respond to them. The first is we don't really bring the Sweden II Trial because of our need for the post-three dose efficacy. We report it, and I think the data are interesting and useful. But the real reason we bring the Sweden II Trial is because of the question as to whether the reduced pertactin antibody response in U.S. kids has important implications for protection of U.S. kids. And with respect to that, the key part of the Sweden II Trial that -- the reason we bring the Sweden II Trial is because the way it unfolded it turns out that we believe you can derive important efficacy data and serologic data after the second dose. And after the second dose, the efficacy of the acellular vaccine was not as good as the whole cell.

DR. FLEMING: Right.

DR. DECKER: But it was more than good enough. No other acellular vaccine that is licensed in the U.S. had any better efficacy against a comparable whole cell. And importantly, this demonstrated adequate relative efficacy to the whole cell after the second dose is in the context of

antibody levels in the Swedish kids lower than in the American kids in the Bridging Study. So the important point we are trying to draw from the Sweden II -- you know, what you say about the surveillance is true. But unless the surveillance was differential or biased, it weakens the power. It doesn't invalidate the comparisons.

DR. FLEMING: We are agreeing -- last comment. We are agreeing completely on the logic of what you are trying to pursue here. You are trying to address the U.S. Bridging studies by putting them in-between Sweden I and Sweden II. I understand that. That is why you are looking at Sweden II. My concern is the reliability of your conclusions about the actual efficacy in Sweden II then is critical to that argument. And with such dramatic under-reporting, there is first of all significant lack of power to be able to derive reliable conclusions. But secondly, also major risks for bias because so much of what actually is happening in terms of the cases aren't being detected. But what we see is an estimate of an increase, but an increase that could be consistent with a fairly striking and unacceptable level of increase. Not because the data are proving that there is an increase, but because there is such variability

due to under-reporting and such potential bias due to that under-reporting. Plus the fact that the point estimate is in the wrong direction over that region where you are drawing our attention, which is after dose 2.

DR. DECKER: I wouldn't characterize it as being in the wrong direction. The key thing is that the estimate of efficacy at that point is compatible with the estimated efficacies of other acellular vaccines that are licensed in the U.S.

DR. GRIFFIN: Okay, I think we have gotten -- unless you have new points to make.

DR. DECKER: I do. One more, please. Let me just remind you that what we have focused on for the last five to ten minutes is only one element of the explanation as to why the CPDT vaccine is suitable for use in U.S. children. If we entirely remove the information from the Sweden II Trial, which I don't think would be valid. But if we did, there is still the other data concerning antibody decay, equivalency of the antibody levels, and even the question on the pertactin is a focus on a difference in one of the four antibodies, and we have got good data to suggest that the protection arrives from the combination of all of the antibodies. And so I don't want the

legitimate argument over the interpretation of the Sweden II data to cause us to forget that that is only one element in a larger picture. Other elements --

DR. GRIFFIN: Okay, we won't.

DR. FLEMING: I would like to address those other elements later today.

DR. GRIFFIN: Okay. Yes. No, we will get back to them. But let's stick to addressing the questions that people have specifically asked. Okay, other -- okay, I just wanted to make sure that there wasn't anybody on this side of the table that I wasn't looking at and ignoring. Dr. Kohl?

DR. KOHL: I think to some extent we may be missing the forest for the trees. And it goes back to a question that Dr. Fleming asked, which is really the key question. And Dr. Fleming asked what levels of antibody are correlated with protection -- I may be paraphrasing him. There is a more basic question to that obviously. It is, is antibody correlated with protection? And this is an extremely controversial part of the whole pertussis story. There are good data in animals that animals given TH-1 cells and no antibodies at all are protected to some extent against pertussis. And we know from some of the other vaccines, the pertussis toxin only vaccine and the

two-component vaccine, which contains no pertactin, that there is reasonable protection, not great, in the PT only and pretty good protection in the two-component. So I think it is a more basic question that we have to address. And I am concerned that we are focusing on this minutia with pertactin when, from what I can see, this is quite an excellent vaccine and I hope that this obsessional concern here doesn't throw us off track of the bigger picture. That we really don't know in 2000, I don't think, which antibodies protect, let alone exactly what level of an antibody protects. So I think we have to bear that in mind.

DR. GRIFFIN: Okay. Ms. Fisher?

MS. FISHER: I want to return to the HHE issue, because that is a very serious event. And in the Swedish II Trials, the HCPDT vaccine was second most reactive in that category. And HHE has been particularly associated with pertussis containing vaccines and speculation has been that it is either caused by the endotoxin or by pertussis toxin. So the CPDT vaccine included in Swedish Trial I contained half the amount of pertussis toxin that the HCPDT vaccine in the Swedish Trial II did. First, do you know the components in the vaccine responsible for HHE

and the biological mechanism. And if you don't, isn't it risky to assume that the increased HHE seen within the Swedish Trial with that vaccine, even with the increased observation, that they were not due to the increased levels of pertussis toxin in that vaccine?

DR. FAHIM: Just one comment. Actually, you raise a very good point. In that same trial, we had another vaccine, the two-component, which had 25 micrograms, which is higher than the 20 micrograms we had with the hybrid combination. So we had 25 micrograms in the one vaccine that compared with the HCPDT and the differences in HHE's are insignificant statistically.

MS. FISHER: That is the DTaP-2?

DR. FAHIM: Correct. That has 25 micrograms of PT compared to our 20 micrograms.

MS. FISHER: And the DTaP-3, what did that have?

DR. FAHIM: That has a recombinant pertussis toxoid. It has 5 micrograms of a recombinant, which is a different -- completely different shape.

MS. FISHER: Do you know what component is responsible?

DR. FAHIM: No. I don't think I do.

DR. DECKER: No. This is -- to the best of my knowledge, no one in this room knows for sure what the connection is between pertussis-containing vaccines and HHE. That is something we would like to know more about but we don't know. With respect --

MS. FISHER: One of the reasons I am concerned is I -- something crossed my desk just this week coming from Canada about the epidemic of anaphylaxis and shock-like episodes after vaccination which could potentially also be HHE. And since this vaccine, the HCPDT formulation is the one used in Canada is the reason I am concerned about the HHE connection here.

DR. DECKER: Well, I have got basically two answers. One is as I said before, and you will all make up your own minds looking at the data, but I am firmly convinced that the elevated rate of HHE reporting in the Sweden II is not a function of this one vaccine. It is a function of the way that study was conducted. But the second thing is if you are not convinced of that, remember that is not the vaccine we bring here to license today. We show you the Sweden II data because, as I mentioned, this discussion with Dr. Fleming. We think it helps to reassure that the CPDT vaccine will be efficacious in U.S. children. But if

you believe that the CPDT is a safer vaccine than the HCPDT, I would remind you it is the CPDT we seek licensure of.

MS. FISHER: I understand.

DR. GRIFFIN: Dr. Hewlett?

DR. HEWLETT: In fairness, it is not really appropriate to refer to this as pertussis toxin. It is pertussis toxoid in these vaccines. Unlike the whole cell vaccine, in which there is some biologically active pertussis toxin. all of these acellular vaccines, to the best of my knowledge, have no measurable pertussis toxin biological activity.

MS. FISHER: Really? That was not my understanding. I understood that there was still some bioactivity with acellular.

DR. HEWLETT: Well, maybe they can answer this.

DR. FAHIM: Based on the assays defined by the FDA, we don't have -- based on the sensitivity of those assays, we don't have any measurable detectable pertussis toxin in our vaccine. Based on multiple assays that we used for the release of this vaccine, we don't have any measurable pertussis toxin.

DR. GRIFFIN: Okay. Other questions from the committee before we take a coffee break? All

right. We will have a coffee break. Let's make it short. Back by 11:15.

(Whereupon, at 11:00 a.m., off the record until 11:17 a.m.)

DR. GRIFFIN: Okay, now we are going to move to presentations from the FDA that are relevant to our discussions today. First, we will start with Dr. Meade on efficacy and immunogenicity.

DR. MEADE: Okay. In this section, I will spend about 30 minutes presenting some review and comment of some of the data that we have looked at this morning. My part of this will be dealing with the efficacy and immunogenicity issues and then following my presentation, Dr. Antonio Geber, the clinical reviewer for this application will discuss the safety and concurrent immunization issues.

So, again, I will start with -- the question that my presentation will be dealing with will be related to the question of efficacy. To remind you that we will be asking the question in two parts. The first one, 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 question 1B, if

the committee response to question 1A is yes, please 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.

I am going -- in this presentation, I will be mentioning two of the safety and immunogenicity trials with CPDT, and I thought it would be worthwhile to mention them very briefly here, because I will switch back and forth a little bit during the talk. The first one you have heard, we presented very briefly earlier, is the U.S. Bridging Study, and that was the Population and Lot Bridging Study, which included the two lots of CPDT, lots 6 and 9. It was done in the U.S. at a 2, 4 and 6 month schedule with this number of subjects and was completed in 1997.

We will also be mentioning the phase II lot consistency study, which again included three lots of CPDT and was done in Canada. And this study, they had children with a 2, 4 and 6 month schedule and that portion was completed in about 1993. And these children received the fourth dose at 17 to 18 months of age and that was completed in 1994.

Again, I will come back and I will try to emphasize which trial I am talking about when I am

switching on this as I go through.

Just to go back now to highlight the points I made earlier regarding the U.S. Population Bridging Study. The study was conducted to compare the antibody responses between U.S. and Swedish infants, to provide immunogenicity data to support the generalization of the Swedish efficacy data to the U.S. infant population. And again, that trial in the U.S. did lots 6 and 9, as we have discussed earlier, and the immunogenicity comparison was done using data, same lab, same time, using children with lot 6 in Sweden and lot 6 in the U.S. and lot 9, which was a more recently manufactured lot in the U.S.

We should mention the antibodies to the U.S. Bridging Study portion were measured initially at Connaught prior to the complete validation of the assays. After completion of validation, APL re-assayed the available sera from the U.S. Bridging Study and from Sweden Trial I. And the sera that were available for this assay included 46 percent of the samples that they had obtained from Sweden and approximately 71 percent of serum samples from lot 6 and lot 9.

And the serology data were submitted in August of 1999. And I will go through -- you have seen some of these data, but I will go through them

very briefly to highlight a few specific points to show that they didn't meet the criteria for either lot when applied to lot 6 in the Sweden Trial I. There was a lower geometric mean and a higher proportion of non-responders and a higher proportion of low-responders. And I will go through the data a little bit more -- some aspects a little bit more completely.

You have seen the reverse cumulative distribution curves and I don't think we need to see them again. But to highlight again that it was different. It differed substantially in shape of the curve. Again, especially at the lower end of the responses.

Again, this is to show the geometric mean data. And you have seen these highlighted in the pertactin data from Sweden I. There were 83 serum samples available with this mean. From the Bridging Study there was 107 available for lot 6 and 108 for lot 9. These are the GMC's and these are the ratios of the GMC's with the confidence intervals -- 90 percent confidence intervals. So comparing lot 6 in the U.S. versus lot 6 in Sweden, the ratio is .54, with the confidence intervals as shown. And again, this shows lot 9 to U.S. and lot 6 to U.S. with the estimate of

.72.

Again, to highlight what I think many of us believe is of particular importance is to look at the low end of the curve. This illustrates for, again, arbitrarily selected values, 5, 20 and 50. The difference in proportion of individuals -- of subjects who met those criteria. In Sweden Trial I, all children had a post-immunization value greater than 20, and only about 10 percent were less than 50 one month after the third dose. If we compare the comparable cutoffs for the lot 6 and 9 for the U.S. Bridging Study, again it was 5 to 7 percent that were below the 5 ELISA unit cutoff, 17 to 22 percent that were below 20, and again approximately 35 to 42 percent that were below the 50.

So the conclusion is that they didn't meet -- you know, they were lower responses in the U.S. compared to what they saw in the regulatory population, and the regulatory issue is that lower responses to an antigen believed important for protection for this vaccine suggest that the vaccine may have a lower efficacy in the U.S. population than what was estimated in the efficacy trial in Sweden.

So we wanted to review a few points along the way. On some of the analyses and evaluations that

have been done related to this, and one of the points -- again, this was due to the age of the lot used in the efficacy studies. And again, in the Bridging Study the lot 6 was about four years old at the time immunizations were done. However, this seems not to be a major issue because the results for lot 6, which was the efficacy lot, were similar to or higher than the results for the more recently manufactured lot 9.

And we asked the sponsor to look to see if this was unique to this particular trial, and Aventis has reviewed data from the other U.S. and Canadian studies and they looked at data from CPDT, HCPDT and combinations that were based on both of these vaccines, and the quantity of pertactin per dose is the same for all of the products. And again in all of these analyses, most antibodies were measured either at laboratories other than APL or at APL prior to assay but finalized by validation. So that has to be kept in mind. But the available evidence from these studies indicates that the antibody responses to pertactin in the U.S./Canadian children were generally lower than those observed in infants from Sweden in Trial I. So the evidence seemed to be that it was not unique to that particular trial.

Again, as you heard earlier, there was

some looking to see if this was potential explanations for that. One, again, looked at the age of first dose. And as the sponsor noted, in Trial I all the infants were at least 60 days of age at time of enrollment. And in some of the U.S. trials, there were some of the infants that were less than 60 days, as you saw earlier. But it is important to note that in most of the Canadian trials, virtually all of the children were at least 60 days of age at the time of entry in the trial. And we saw some data from the sponsor suggesting that at least in one analysis the maternal antibody in the pre-immunization sample could potentially be influencing the results. Again, in the U.S. studies, possibly related to the lower age at obtaining the pre-immunization sample. But also potentially other explanations, there was again higher maternal antibody in the U.S. studies. And at least in the one study -- one of the studies is that there was a negative correlation between the pre and post-dose three pertactin antibody responses, suggesting that the maternal antibody could somehow influence the results. But we have looked at, again, the information of the sponsor and we have looked at most of the North American studies, and we are not finding a consistent conclusion that can be drawn in all of the studies.

For example in the MAPT trial, there was no significant negative correlation between pre and post-immunization titers for pertactin antibody.

So, again, if it were a consistent observation from all of the trials, that would be -- at least would provide an explanation. But we have not at this point seen a consistent conclusion. But again, we are certainly willing -- you know, further explanations and studies to try to evaluate that would be useful. Again, I am not sure how it could influence immunization practices. We are certainly not going to be screening mothers for antibody -- prior to immunization. So again, I think there is some question about how it influences practices, even if we do have an explanation.

So we wanted to look at little bit at the issue we have talked about before as to what is the clinical significance of reduced responses. And we wanted to talk through some of the analyses that have been presented. And one relates to the household contact studies that were designed to look for correlates of immunity. And there were two published studies back to back in vaccine. One from Storsaeter, et al. That was the data you have seen before already this morning from Sweden Trial I. And there was a

study by Cherry, et al., that used data from a German trial that evaluated the Acel-Immune product. Both of these studies concluded that when exposed to pertussis, the lowest pertussis attack rates were observed in children with detectable antibodies to protect and fimbriae and to a lesser extent for pertussis toxin.

However, it is important to note that there is no serologic correlate of immunity that has been universally accepted for acellular pertussis vaccines for some of the reasons that I will talk about in the next slide.

And in particular, at least in some of the submissions we received from the sponsor -- I don't think they did so today -- and the question is is there a protective level. In some of the submissions, the value of 5 ELISA units was suggested as a protected level, and that was the cutoff used in the household contact study that you heard this morning. But I think we need to keep in mind some of the limitations of any value, again much less 5 ELISA units for defining protective level. One is that the household contact studies evaluated the concentration as well as possible at the time of exposure and not at the post-immunization time point of one or two months

post-immunization. And the two household contact studies, the two of them used different values to define what they specified as a threshold response. Similar, but again not identical. And again, the values were measured in different laboratories. So the absolute antibody values may not be equivalent in the different laboratories. But more importantly, I think it is important to know that these are observations based on pre-immunization samples. But it doesn't begin to evaluate and really discuss the relative contribution of each individual antigen to protection and this has not really been elucidated. And again, even we will recall that the protective mechanisms, as was mentioned this morning, are not really fully understood. Is it antibody or is it cell mediated immunity or some assessment of memory that can occur in response to infection. So, again, in the absence of a clear understanding of protective mechanisms, just a simple interpretation of antibody, any antibody value as being protective, I think needs to be thought through carefully.

Again, related to the evidence that -- again, this is, as you have heard this morning, APL has presented evidence to support efficacy in the U.S. population. In our reviews, we have broken these down

into three areas for our purpose of review. One is the argument related to the redundancy of the pertussis component with basically the argument being that with the multi-antigen vaccine, children may not need to respond to all antigens in order to be protected.

Secondary, which we have heard this morning, is that there is efficacy in a population that had heterogeneous responses to protect, and this was based on the data we saw this morning based on Trial II, the safety immunogenicity of the HCPDT vaccine after two doses.

And then the third area relates to their presentation for the adequacy of pertactin response following the fourth dose. And the argument is that children respond adequately to pertactin following the fourth dose recommended in the U.S. schedule.

Now I wanted to start with the last of those, which again I think will be the first part of our question. It relates to the fourth dose and it certainly is a lower hurdle for evaluating the data. And APL has concluded that the pertactin antibody response following the fourth dose in North American toddlers is equal to or greater than that observed following the three-dose series using the Swedish efficacy Trial I.

Now related to this, I wanted to note that Aventis was not able to evaluate the response to the fourth dose schedule in the U.S. Bridging Study, which is the study we have been looking at, because no subject received a fourth dose of CPDT. We should note that some children received an investigational vaccine for the fourth dose. But again the data from this investigational vaccine has not been considered relevant to this application.

Since the data from the U.S. Bridging Study were not available, APL has submitted post-fourth dose immunogenicity data from four other studies. For the largest study, the sponsor was able to go back to a phase II study, which I will describe on the next slide, and reanalyze the pre and post-fourth dose sample using the revalidated assays. For the other three studies, antibody assays were performed either by a different laboratory or by Aventis prior to completion of the validation.

. I am going back to this slide again just to keep in mind which study we are talking about. This is the U.S. Bridging Study. Again, there are no fourth dose data. The largest study with fourth dose data is the phase II, which was designed as a lot consistency study in Canada in which they had data on 301 subjects

at the 35 infants who had the lowest post-dose three pertactin antibody. Again, this was the pre-validated assays. So we were not accepting them in a quantitative sense, but we ranked them and picked the 35 infants that had the lowest, and this value was those that had less than 5 ELISA units after the third dose. And again, looking at these 35 specifically, the geometric mean post-dose four was 125 ELISA units with the confidence intervals indicated. And of these 35, all of these infants had exceeded the 25 ELISA unit threshold cutoff after the fourth dose.

And then just to complete the available data. The fourth dose data are presented here. It is three smaller studies. And here we present the results post-dose three, post-dose four. We indicate the laboratory that did these assays and the number of individuals. And again, because of the differences in laboratories and the fact that the assays at APL were prior to completion of the validation, again we need to be somewhat careful in comparing these. But in all cases, you will see that there was certainly a good measurable response post-dose four that was higher than that observed post-dose three in all of these studies.

So that summarizes what is available on

the fourth dose. I want to move to some of the areas of argument that have been presented by the sponsor. And the first relates to the redundancy of the pertussis component. We have reviewed it contains five antigens, as we have discussed. And APL has proposed the responses to all the antigens are not necessary for protection. And specifically that reduced response to one of the antigens would not necessarily put a child at risk of infection.

So, again, we have done some analyses to look at -- to break this down and to try to look at that a little more clearly as to the response of the other antigens in these subjects. And this was analysis that was done by APL at our request. What we have looked at is we -- now we have gone back to the U.S. Bridging Study -- again, just to remind you that this is the Bridging Study that showed the low responses in the RCDs shown earlier. Again, what we have done is we have stratified the children for each of the lots that you have used based on what their pertactin response was after the third dose. We have chosen a very arbitrary cutoff of 20 ELISA units, and we have chosen that -- probably the primary reason is that it is well above the limit of quantitation in the assays and it is not a close call. It is certainly a

measurable quantifiable response. It is on the low end, but still it is a quantifiable response. And we thought this was a reasonable cutoff. They have looked at other cutoffs, but this is an arbitrary one that seemed to make some sense.

If we look at those who had less than 20 after the third dose, we look at the responses to the other antigens and compare them to those who had greater than 20 ELISA units to protect. And the trend is certainly true in all of the assays that those subjects who had a lower response to pertactin tended to have a lower response to the other antigen. And that held true with both of lots 6 and 9.

So given the -- again, this information we have at this stage, we took their line listings of data and actually thought it was important to look at individual study subjects. Again, the cutoffs are arbitrary and we thought it was important to look at the responses more carefully. And this is analyses that we have done from their line listings of data. And for the 215 subjects immunized with CPDT, and we have lumped lots 6 and 9 in this analysis for simplicity. And, again, for those for whom sera was available for reassay, we observed that 72 percent -- again, going through the same arbitrary cutoff, which

again is well above the LOQ in all four assays -- sorry, limit of quantitation in all four assays. 72 percent were above 20 for all four assays or for all four of the antigens tested. 93 percent of the subjects had greater than 20 ELISA units for at least three of the four antigens. And 98 percent had at least 20 ELISA units against at least two of the antigens. Again, in our reevaluating these data, it appears to us that at least most of the individuals responded to more than one of the pertussis components. And again, we have looked at the line listings in more depth, and of the values, the relative few values that were below the limit of quantitation, which is again the lowest quantifiable of antibody. And again in looking at the line listings, all of the infants were above the LOQ, again quantifiable antibody, in at least two of the antibody assays. Again, there were relatively few values below the limit of quantitation.

But again, I think it is important, as we will hear -- we have heard this morning and we will hear again -- it is very difficult to interpret the clinical significance of these observations in the absence of a well defined and validated serologic correlate.

Now I wanted to turn to the third area that we have had discussed this morning by the sponsor, and that relates -- again, the way we have presented this is that the sponsor has tried to make a case for efficacy in a population with heterogeneous responses to pertactin using the data as we have seen from before on Trial II in Sweden. And again, as we have heard already, that employs the efficacy and immunogenicity data following the second dose of HCPDT given at five months of age.

By now I think you are well familiar with the layout of Trial II, but again to remind you it was a 3, 5 and 12 month schedule. There was a minority, about 12 percent of the subjects that were evaluated on the 2, 4 and 6 month schedule. This lists the vaccines that were evaluated. And the result, which has been presented, that the efficacy with this definition was comparable to the whole cell vaccine with these relative risks indicated.

But the analysis that has been presented today is not what was defined as the primary analysis from the trial. It was a different efficacy analysis. This was a planned analysis that was done at the 7 month interval following the second dose of HCPDT given at five months of age. And the data we have seen

this morning is that for the interval for 5 to 12 months of age, the efficacy for HCPDT was significantly greater than that for the two-component vaccine, the SKB two-component vaccine with the relative risks as listed. The quantitative antibody comparisons that have been done in these analyses compare the Sweden Trial II results, which the samples were taken two months after the second dose and compared to the data from the U.S. Bridging Study, which again was one month after the third dose. So we have a difference in the timing of samples.

And I think it is important to highlight some of the limitations that we have identified for these analysis. Again, I think many of these have been brought up this morning, but I wanted to comment that the vaccine composition was different. That the hybrid vaccine contains more of an inactivated pertussis toxin and FHA than the CPDT. And it is important to keep in mind that the duration of protection was really only this 7-month period of observation -- again, that interval between 5 to 12 months of age. And the efficacy was reported relative to other vaccines. Again, it was done to the two-component vaccine for which the absolute efficacy following only two doses is uncertain.

Again, there were differences in the antibody testing laboratories. The Swedish data were from the Swedish laboratory and the North American studies were from the APL laboratory. We have seen some data this morning indicating -- in which they showed the different -- the similarity of assays and results from the assays. But again, one of the important issues is the timing of the serum sampling and making any comparison. It was two months post-dose two versus one month post-dose three, and they use comparisons. And I think this timing of serum sampling is important. Again, in the analyses that we were presented related to this in making these comparisons, APL employed antibody decay rates that were estimated from observed published antibody values. The estimated decay rates were then used by APL to estimate the antibody concentrations. And they would estimate the concentration at one month post-immunization when the two month value was available or at two months post-immunization when the one month value was available.

Again, I think it is important to point out at least some of the limitations to the quantitative use of these decay curves. Again, I think the validity of the estimated decay rates has

not really been rigorously verified in studies. The Swedish investigators concluded that in the publication that the decay rate estimates were of limited predictive value for any individual. The decay rates were estimated based on three observed time points. The one month, seven month and 23 month post-dose three data points. And it assumes a linear decay during the relevant interval and the comparisons between one and two months post-immunization.

Our conclusion is that the quantitative comparisons between the U.S. Bridging Study and the Sweden Trial II have important limitations. Again, on the other hand we have looked at the qualitative comparisons from the sponsor and what we have done -- and I will show our CD on the next slide. For the pertactin antibody, they compare the RCD curves among the subjects -- and again, they were looking at the shape of the curves in the U.S. Bridging study, which are the curves you have seen many times already this morning -- lot 6 and 9 -- one month post-dose 3. On the same graph we will show the data Sweden Trial II, two months post-dose two. And on this same curve -- again, it was from the sponsor and included two other curves. I thought I should identify them. These were from Swedish infants done in the Swedish laboratory.

These were one month post-dose three. And this included the data from Sweden Trial I at the 2, 4 and 6 month schedule. And as you recall, that minority group had 12 percent of the population. In the Sweden Trial II, they were evaluated on the 2, 4 and 6 month schedule, and this is from the immunogenicity subset from that group.

Again, this shows the RCDs. Again, the two on the right are the two that are one month post-dose three from Sweden Trial I, which is lot 6, and Sweden Trial II, which was at 7 months of again but it was following the 2, 4 and 6 month schedule. So these two are presented for comparison. And the other three curves are shown here. Again, you have seen lot 6 and lot 9 this morning several times from the U.S. Bridging Study. And this superimposes the data, non-adjusted. Again, we feel that adjustments are really of limited value. So these are the non-adjusted values for two months after the two doses in Trial II. Again, this is the 7 month time point in the two month schedule. And again, since it is two months after the dose versus one month after the dose, we certainly expect that there would be some shifting of this curve to the right. Again, but we wouldn't begin to know how far to adjust that very accurately.

But I think the conclusion from this is again that the shape of the curves are similar in that you have a population in Trial II in Sweden that has a very heterogeneous response to pertactin, and again some individuals that had very low or no responses. And it is roughly similar to the shape of the curve as has been seen from the U.S. Bridging Study.

So with respect to these qualitative comparisons, the conclusion by the sponsor is that the comparable RCDs indicate heterogeneity among subjects in the response to pertactin in both Sweden Trial II, which are again two months post-dose two, and the U.S. Bridging Study one month post-dose three. And they have concluded that the data provide evidence for efficacy in a population immunized with the Aventis pertussis antigens but without antibody to all of the antigens. And in any kind of evaluation, it is important to remember that in each case they would be receiving doses of DTaP. In Sweden Trial II, the subjects did in fact receive their third dose at 12 months of age. And in North America in the U.S., a fourth dose is recommended at 15 to 20 months of age in that group.

So again, I just want to conclude with the -- again, what I have tried to do is summarize some of

our comments and thoughts related to some of the analyses presented, again in what was our interpretation of the three areas of argument that have been presented by the sponsor related to this. One as it relates to the redundancy of the pertussis component. One is the efficacy in the population with heterogeneous responses to pertactin. And then the -- as we have summarized before, the response to pertactin specifically following the fourth dose. That concludes my presentation.

DR. GRIFFIN: Okay. Thank you. I think we will have questions now for Dr. Meade. Yes, Dr. Huang?

DR. HUANG: Why don't we see any protective efficacy studies from the Bridging results, even if we have to compare them to historical controls or other types of controls?

DR. MEADE: I am sorry, I couldn't hear you. I am sorry.

DR. HUANG: Why don't we see any protective efficacy results from the Bridging studies, even if we have to compare them to historical controls or some other types of controls? There is no pertussis in the United States?

DR. MEADE: No, no.

DR. HUANG: So there is no way that you

can get any direct result like that?

DR. GEBER: There were only 315 subjects enrolled in that study.

DR. HUANG: Right.

DR. GEBER: As clear -- I think the group from NIH can tell you, when they were looking for places where they could do efficacy studies, they evaluated whether or not studies could be done in the U.S., and the conclusion is that there was not enough pertussis in order to do a trial here. And certainly not in the number of subjects that were done in the safety and immunogenicity studies.

DR. GRIFFIN: Other questions for Dr. Meade? Dr. Estes?

DR. ESTES: I would just like a clarification about -- could you explain to me why we don't have a correlate of protection? Are people working on this? Briefly, just update me.

DR. MEADE: That is a very good question. I am trying to think --

DR. GRIFFIN: Some member of the panel want to address that one?

DR. MEADE: You can pick several different answers. Again, we could cover the rest of the afternoon, and in fact there will be -- NIH is holding

a pertussis meeting in about a week and a half and that will certainly be one of the topics that will be updated and discussed at length. But I think there is at least two types of explanation that I can come up with. And again, I would invite any others on the panel. One is that there is multiple antigens. Again, we have seen from this that in the U.S. there are vaccines of different composition. So there are certainly different -- there has been data that shows that a one-component vaccine can be effective and a two-component and a three and a four. So, again, it is very complex in terms of the composition. So it is very complex. If we had one antigen and enough data, you could certainly look at it more carefully. So it is very complex just in terms of the number of antigens and doing multi-component analysis with trying to -- when you have different antibodies to put them all together. And the best available data is what was presented in the household contact studies that were included in the briefing packages.

But I think the other important area is that if you look at the data that is available from animal models and available human data, it is certainly very complex. There is certainly evidence that cell mediated immunity is very important. Again,

there is good evidence that in some models and in some systems you can get protection in the absence of antibody. And again, the other component that is very difficult to evaluate in my mind is memory. Again, if you are primed for a booster response, upon exposure you can presumably mount an antibody response. And it is very difficult to measure memory and quantitate memory and do any comparison. So it is -- those are at least the ones that I can come up with quickly. And I would certainly invite other members of the panel if they wanted to comment on other reasons why it has been difficult. It is certainly being looked at. There has been -- it has been looked at exhaustively. I think the data that are available today are -- is the best available information.

DR. GRIFFIN: Other questions? Yes?

DR. HEWLETT: I will just add a little bit. I think that was a very good summary of what the situation is at the present time. There are multiple antigens that are important here. The problem with the original Swedish field trial was the timing of the collection of the sera after -- there was not a pre-exposure estimate available. Therefore, there was not any apparent serologic relationship between who got disease and who didn't. What we see from the papers

that are included here -- interestingly from two separate studies -- is that there are some relationships. There are not as there are for other infectious disease processes values in which you can pretty much define a threshold as of yet. But certainly there are relationships. And that is a big step forward over where we have been in the past. But I think we certainly see patients who recover from pertussis who have not made antibody against pertussis toxin. And we have other people who don't have antibody against pertactin. So the host response is heterogeneous. What is needed for immunity undoubtedly is heterogeneous. So it is very complicated. Probably if you have a little of this and less of that, it will work. And if you have more of this and less of that, it will work. And if you have more of both of them, maybe you are better off.

DR. GRIFFIN: Okay. Dr. Fleming?

DR. FLEMING: I found it interesting in reading the document. There was a statement that says, "In the absence of an accepted correlate of immunity, a demonstration of comparable antibody responses would provide support for the conclusion that efficacy was likely to be comparable in both populations." It seems to me the latter is a non sequitur of the former. And

in fact, the very thing we are hearing here -- it is undoubtedly a multi-faceted mechanism of action issue here. So relying on antibody responses, which is essentially what the latter part says here, seems to be a real reach or a real act of faith here in the absence of any really scientifically rigorous justification for that.

One of the things, though, that there does seem to be at least some clue about is you had given us the numbers of these participants that had achieved adequate units for at least two antigens and at least three antigens and at least four antigens, and you said it wasn't clear how many you needed. But 98 percent had had adequate EU responses for at least two antigens. Again, I don't know what we consider adequate efficacy, but one solid result we seem to have is from the Sweden I Trial that indicates that there is a difference in efficacy between the two-component Infanrix vaccine and the five-component APL vaccine, where the efficacy difference went from 58 to 85 percent. What is interesting is the five-component vaccine achieved that 85 percent efficacy compared to the 58 percent efficacy of the two-component FHA and PT containing vaccine, even though it had discernibly less GMTs for PT and FHA. As you went from the two-

component Infanrix vaccine to the five-component APL, the CPDT vaccine, the GMTs to PT dropped from 60 to 49 and FHA dropped from 111 to 34. And yet the five-component vaccine had better efficacy. It is telling me that two antigens isn't enough. Or you can certainly do a lot better with more than two antigens.

DR. GRIFFIN: Okay.

DR. MEADE: I need to make one important clarification. In those analysis, we picked 20 and it is an arbitrary, I would not want to use the word adequate for the reasons we have talked about before. But we picked our 20 as clearly quantifiable in response. Again, for the reasons you say, I would avoid using the word adequate. It is above the 20 cutoff, which we use again to just try to identify the types of responses we were seeing. We did analyses breaking down by which antigens, which is again -- so that has -- we have looked at that also, which is again an important issue. One potentially to which -- not only which antigens, but how much. But that is --

DR. FLEMING: Sure. Understood. Your analysis that used 20 ELISA units as the cutoff giving us 98 percent having at least two antigens is arbitrary. But your fundamental question is -- the question you posed was is two antigens enough? Is

three antigens? Is four antigens? And what I am arguing is the one thing we actually have firm data on is a randomized comparative trial in Sweden I comparing the two-component against the five-component. And even though the five-component achieved much lower GMTs to the two antigens in the two component, it achieved a much higher success rate. Which suggests to me that ultimately I don't know whether it is measured by serologic response, but ultimately the other two components here, specifically the pertactin and the fimbriae, do seem to be important to the overall achievement of higher efficacy.

DR. KOHL: That is really important, Tom. And I think one of the things you have to be extremely careful with these pertussis trials is keeping each trial separate. And what you are seeing I think in that trial is a good vaccine which happens to have five components against a lousy vaccine which happens to have two components. But I don't think you can generalize from that trial that two components is half as good as five components or two-fifths as good, et cetera. There is a one-component vaccine in a nice tight trial that had a 70 percent efficacy rate -- PT alone. There is a two-component vaccine in a

reasonable trial that had an 80 something percent efficacy rate. So you really have to be careful when you try to generalize from one study or even across the board, because the studies are so different. And I guess I would like you to address that because you are trying to make some correlates with these antibody responses, which we know very little about anyway. And yet we do have a one-component vaccine and a two-component vaccine that are currently licensed in this country that have very low antibody responses to pertactin and to fimbriae because there are none in it. Yet, they are licensed and they are proven efficacious. So why are we putting so much emphasis on this one antibody level.

DR. MEADE: Again, I think the analyses we have done is we have agreed we can't compare between products. The only objective analysis we have is what are the data for this product in the efficacy study and then what are the data for that product in the population where it is going to be used. When you get comparable responses in the assays we know how to measure, then -- but when you see differences, I think the concern or the question relates to the fact that there is such a significant proportion of the population that had no response to pertactin in the

U.S. And if pertactin is an important component of that vaccine and you see a lower response to that in the U.S. population in the one response that is available for pertactin, it makes it difficult to assume that the efficacy seen in the trial directly would be seen in the U.S. I mean, the one objective comparison we can make is what does that vaccine do in the U.S. And the significance of that is a very complex question that we have been struggling with and in fact is why we are here at the Advisory Committee meeting because it is such a complex question.

DR. GRIFFIN: Ms. Fisher?

MS. FISHER: Well, when you take your child in today to the doctor to have a blood test for proof of immunity to pertussis, you get a PT and an FHA reading. So what we are being asked to do here --

DR. GRIFFIN: I don't that -- is that done? Is that part of pediatric? I don't think that that happens.

DR. MEADE: I am not aware of that and I wouldn't know how to interpret it myself. I wouldn't --

MS. FISHER: Well, I can bring you lab reports.

DR. GRIFFIN: But I don't think most

people bring their children in to get antibody tests for these antigens I guess is my only point.

MS. FISHER: But post-pertussis disease, you do get a lab test.

DR. MEADE: That is diagnostic, right.

MS. FISHER: Diagnostic, right. For confirmation of pertussis.

DR. MEADE: Right.

MS. FISHER: And they give you a PT reading, pertussis toxin reading, and FHA reading. Which is --

DR. MEADE: It is possible to do that.

MS. FISHER: With levels -- okay. So it just seems to me that pertussis toxin and FHA have been the traditional components you look at.

DR. GRIFFIN: No, no. That is only for diagnosis. It is not for looking at protection. I mean, that situation you are talking about is for diagnosis of disease, not looking at who is protected. Those are two different questions.

MS. FISHER: Well what is -- then what is confirmation of protection?

DR. GRIFFIN: That is basically what we have been talking about. Nobody knows for sure. And that is what these trials are trying to address.

MS. FISHER: But there had to have been some standard prior. I mean, we are being asked to look at pertactin. You say lowest pertussis rates in children with detectable antibodies to pertactin, fimbriae and to a lesser extent pertussis toxin. That is the argument that is being made here. That this vaccine is efficacious because those readings are high in those children who have low pertussis rates, correct?

DR. GRIFFIN: Well, I mean the main focus of the discussion is that we do not have solid data on how the antibody levels relate to efficacy.

MS. FISHER: That is right. So how -- if we do not have something that we are starting from, how can we possibly pass off on this?

DR. MEADE: I think it is important to remember -- and the sponsor could comment on this -- that there is efficacy data for this product. I mean the decision, the primary starting point for any decision is have they been able to demonstrate efficacy for the product in an efficacy study looking at protection from disease, which is the data that has been submitted and that is from the Sweden Trial I. That is the data that speaks to the efficacy of the product. But that addresses the efficacy in Sweden

and one of the questions relates to can we make conclusions that would be comparable effective in the U.S.

MS. FISHER: It is extremely important because if you have a difference in populations and you have higher maternal antibody levels in the United States and you see a lower pertactin response, if you do not understand the mechanism of either the disease-induced immunity or the vaccine-induced immunity, there is no way to measure.

DR. GRIFFIN: I think that is the reason that it has been brought to the Advisory Council as a complicated issue. You have to balance a lot of different pieces of information, none of which are absolute. I mean, there aren't absolute levels. So that is the reason they ask for the advice of people who think about these things. Okay, other questions?

DR. LIVENGOOD: Just briefly. I mean, sort of taking a more historical perspective. When we were first designing these trials, there was a concern on the part of the community, the public health community, that even after these trials in Sweden, Italy and Germany, places that have pertussis, that we would have a barrier to licensure of the vaccines in the United States since we would not have efficacy

data from the United States. We made an informal but nonetheless I think somewhat explicit agreement that we would accept that through the use of these bridging studies where we could demonstrate for each vaccine in and of itself a comparable immune response to that which was generated in the context in which efficacy was demonstrated that therefore we would accept that vaccine for licensure.

Why we are here today is that in the fact of that agreement we have one component which has failed that criterion. Is that a component that is important? We have some data to suggest that some people expert in the field of pertussis through these household contact studies feel that it is very important in this vaccine or in other vaccines. Yet, it is clear that we do not have definitive information one way or another to say that this component or X level of this component is that. So we have sort of ended up in this position where we are going to have to no --

DR. GRIFFIN: Or are we going to get that information? I mean, that information is not accessible.

DR. LIVENGOOD: That is one of the possibilities here. I mean, we have to either decide

that the original agreement by which we would accept these based on immunogenicity data, while it was effective and has certainly moved these vaccines into use in the United States more quickly than one would have had with a different standard, was inadequately thought out and we should reconsider whether we agree that it needs to meet the same immunogenicity criteria. Or we look at the corollary lines of evidences that the FDA and the sponsor have put forward to us today or we request additional information. I think those are where we are going to spend the rest of the afternoon talking about it. So I think you are exactly right with some of the points that have been brought up here. Nobody has a clearcut answer to this or else the sponsor and the FDA would have --

DR. GRIFFIN: It wouldn't have been so hard.

DR. LIVENGOOD: Right.

DR. GRIFFIN: Okay. One more comment and then I think we will move on to the next presentation.

DR. FLEMING: Just to follow up on that and to probe with Steve for a minute. As you point out, if there is an agreement, even if there is uncertainty as to the scientific basis for that

agreement, th at serologic responses and equivalent immunogenicity by those measurements would be used in a bridging sense, and we see, to use your words, that we failed that relative to one of the components, then it becomes important to try to understand whether that component is key. And, Steve, I had mentioned that one of the most solid pieces of information I could think we could get would be a randomized trial between a setting in which the one component wasn't delivered versus where it was delivered and then look to see in that randomized trial whether there is an increase in efficacy. We come pretty close to that because in the Sweden Trial, we have the PT and FHA and then we have the addition of the pertactin.

DR. KOHL: They are different vaccines from different companies. If you had the PT and FHA from the same company and then just added pertactin. But you really can't compare the vaccines otherwise.

DR. FLEMING: Understood. But let me probe with this just a little bit more. You are right, that is the case. And what is interesting is the vaccine that includes the pertactin yields much -- if we are going to use serologic measures, yields much less impressive serologic response to PT and FHA. So isn't that about as close to solid evidence that we can get

that there is something about the pertactin that can in fact substantially increase efficacy?

DR. KOHL: No. Because there are multiple other antigens that we are not testing for, both in cellular immunity and humoral immunity that we are not accounting for at all in that, number one. Number two, even though the levels are lower, it doesn't mean they are not protected. I don't know that there is a threshold protective level versus a curve of protection. I mean, it is so complex because we are talking about thresholds versus curves of protection versus combinations of these curves.

DR. FLEMING: But as soon as we acknowledge this -- and I really understand your point -- but as soon as we acknowledge that there is this myriad of additional types of responses, cell-mediated immune responses and memory and all this, then we are completely throwing away the basis for using the antibody response as our bridging. Do we believe it in any way or do we not?

DR. KOHL: I think the best we have so far are the two papers that have been referred to here. And if you look at those, they are fairly preliminary pieces of data. And that is after ten years of looking very hard for this, it is starting to come. And this

may be the beginning of it. But right now, I think it is soft. It is nice having the experts on the other side, because you guys agree that it is at this point still on the soft side.

DR. HEWLETT: Absolutely. I think the other thing we need to bear in mind is that these data weren't -- data such as they are -- these relationships have been established. And I believe that there are relationships there. Exactly what they mean, whether they are surrogate for something else, is not clear. These relationships exist. We -- you -- whoever didn't have even that level of observation when the previous acellular vaccines were evaluated. They were looked at differently. And I think we have to be careful, as you said before, that this provides guidance to us and enables us to think about it, but doesn't provide a barrier -- put up a new barrier that only confuses the issue.

DR. GRIFFIN: Okay, Dr. Katz.

DR. KATZ: I think Erik has articulated the difference between standards that have been applied and I would put out a rhetorical question to John Livengood, which is if you go by these standards and you say a diminished response to pertactin is important, would you withdraw the approval of the

vaccines you have already licensed that are acellular pertussis vaccines that have no pertactin and have no antibody or minimal antibody responses to pertactin? If you barred this vaccine on that basis, you would be totally inconsistent in what you have done on the past. I wasn't on the committee, so I don't have any institutional history.

DR. GEBER: I think maybe perhaps from FDA's point of view that those vaccines were evaluated in efficacy trials and bridging studies were done to U.S. populations with those vaccines. I think the difficulty we are facing today is that the vaccine was evaluated in an efficacy study and the bridging study did not show comparable. So I am not sure that --

DR. KATZ: But they don't have pertactin.

DR. GEBER: They don't have pertactin, but they were demonstrated to have efficacy without it.

DR. KOHL: What we are seeing is interesting. Having been on the committee for several years. The more complex the vaccine gets and the more components that are involved, and especially when we are looking at combo vaccines or concomitant immunization, typically one thing doesn't make the cut. And what we have done in the last year is knock off a couple of vaccines which some people may

consider good vaccines because one thing didn't make the cut out of four or five or six or seven different tests. And how often does that just happen by chance or by some non-relevant factor that may have no effect on efficacy. I think we are getting into that. Because the more complex these are, the harder it is to prove that they are equal to something in the past.

DR. GRIFFIN: Okay. Should we move on to the next presentation -- the last one of the morning?

DR. GEBER: Good morning or perhaps early afternoon. I will be reviewing the safety data submitted in support of CPDT as well as the data submitted in support of compatibility of CPDT when given with other routinely recommended childhood vaccines.

With regard to safety, the question the committee is being asked to address is are the data adequate to support the safety of CPDT. Please specifically address both the infant series and the fourth dose data. If not, what additional information should be requested?

In support of safety, the sponsor submitted data from clinical trials with CPDT as well as data from clinical trials with the higher antigen component vaccine, the hybrid vaccine, or HCPDT as it

has been referred to today. The FDA's review of the data from the hybrid vaccine focused on serious adverse events following receipt of that vaccine. In my presentation today, I will review the safety results from Sweden Trial I, the results of a phase II lot consistency study. I will summarize the data for local reactogenicity following a fourth consecutive dose of CPDT from several studies, and I will review serious adverse events following receipt of both CPDT and HCPDT. Finally, I will review the available data on the use of CPDT with concurrent immunizations.

Just a brief review of the slides of the safety data base with the CPDT. A total of 3,852 infants received approximately 11,500 doses of the vaccine within the infant series, the vast majority on the U.S. schedule of 2, 4 and 6 months of age. 637 infants received a fourth dose of CPDT and 526 of these received it following an infant series of CPDT. The sponsor is seeking an indication for a fourth dose given at 15 to 20 months of age. However, note of the 526 who received a concurrent consecutive fourth dose of CPDT, only four of them had received it prior to 17 months of age.

I would now like to review the results from the Sweden Trial I. As has been reviewed today,

this was a double blinded, multi-center, randomized DT controlled study. Infants were randomized to one of two acellular pertussis vaccine or DT control arm, and two months into the study to a whole cell vaccine group when that vaccine became available. Analyses of safety included all children as randomized. Adverse events were monitored through the use of diary cards, which parents were instructed to fill out 14 days post-vaccination, and adverse events were collected by scripted telephone interviews on day 1 and 14 post-vaccination. Serious and adverse events and contraindicating adverse events which will be described later and hospitalization records were reviewed throughout the study period until 60 day post-dose three, or until 8 months of age if the child received only one or two doses of the study. All deaths that occurred during this study were recorded.

Shown on this slide are the rates of local reaction reported following the three doses of vaccine for the CPDT arm. As can be seen, there were some increases in reports of induration and redness following successive doses.

However, for all doses, rates of local reactions occurred significantly less frequently following the CPDT vaccine as compared to the whole

cell vaccine, and this is illustrated on this slide for the third dose. Furthermore, rates of local reaction reported by the CPDT group were similar to those reported by the DT control arm.

This slide illustrates selected systemic reactions reported following receipt of CPDT vaccine. While most reactions did not increase in frequency with successive doses, the rate of fever greater to or equal to 30 degrees centigrade did increase with successive doses. And as I will review in the later section, with a second and third dose approximately two-thirds of the children received IPV and one-third received hemophilus conjugate vaccine, whereas only a handful had received these vaccines in the first dose.

Again, systemic reactions were significantly less frequent in the CPDT arm as compared to the whole cell arm, as is illustrated in this slide for the third dose. Furthermore, again, the rates of reactions for the CPDT arm were comparable to those in the DT control arm.

I would now like to review the rates of local reactions in the phase II lot consistency study. I am reviewing these results because it is the largest study in which children received four consecutive doses of CPDT. The lot consistency study was a multi-

center, double blind, randomized study in which children were randomized to receive one of three lots of CPDT or a licensed Canadian whole cell vaccine. Monitoring for safety was accomplished by telephone calls from study personnel to parents at 2 to 6, 8 to 12, 24, 48 and 72 hours post-vaccination, as well as day 7 post-vaccination. Adverse events were also queried in clinic prior to the second and third immunizations and 28 days after the third and fourth doses.

Reaction rates for the CPDT lot were similar and results have been pooled. As you can see in this table, rates of local reaction occurring within 72 hours were higher following the fourth dose as compared to previous doses. However, when reaction rates were compared to the whole cell arm in the fourth dose, the reaction rates were any tenderness, any swelling, any erythema were higher in the whole cell arm as compared to the CPDT arm. But rates of severe swelling and redness were not significantly different among the two groups.

Just to note that for systemic reactions, the increase in reaction rates were not reported in the CPDT arm with successive doses.

FDA requested additional information on

all children who had received a dose of CPDT at 15 to 20 months of age and who had experienced severe local reaction. Severe redness and swelling were defined as reactions of greater to or equal to 35 mm in size. Information was specifically requested regarding the size and the duration of the reactions, the extent of limb involvement and interference with activity and whether the child had received CPDT or whole cell during the infant series. Line listings were provided for all children with severe local reactions and for subjects enrolled in four clinical trials, the FDA was able to identify that the child had received CPDT in the primary series. All studies had follow-up for local reactions at 72 hours and one or two had follow-up -- I am sorry, I believe it was two had follow-up at 7 to 10 days.

Of the 401 subjects enrolled in these four studies, approximately 20 percent experienced redness greater or equal to 35 mm during the first 72 hours. In 4.5 percent, the size of the redness was unchanged in size or was increasing from the previous measurement at the 72 hour follow-up time point. 11 percent approximately reported swelling of greater or equal to 35 mm in size, and in 3 percent, the size of the reaction was either unchanged from the previous

measurement or was increasing in size at the 72 hour follow-up. No specific information was available on the extent of limb involvement or interference with activity.

So I would now like to move to the review of serious adverse events and contraindicating adverse events reported from clinical trials of CPDT and the hybrid vaccine. As has already been reviewed today, the safety and efficacy of the CPDT or classic formulation was studied in Sweden Trial I, and the hybrid vaccine was studied in Sweden Trial II. I have already reviewed the procedures for monitoring safety in Sweden Trial I. Trial II was a randomized, multi-center, double blind study of three DTaP vaccines and a British whole cell vaccine. Approximately 83,000 subjects were enrolled.

Surveillance for serious adverse events was performed by weekly review of hospital records for pre-specified conditions. Parents were asked about the occurrence of serious adverse events and contraindicating adverse events at the time of the second and third dose of vaccination and at a clinic visit when the child was 18 months of age. The vaccination schedule for most children in this trial was 3, 5 and 12 months of age.

Definitions for serious adverse events and contraindicating adverse events were pre-specified for both studies and are listed here on this slide. There were some differences in the definitions for these adverse events, but in general the types of adverse reactions are defined as contraindicating or serious were similar between the two studies. I would like to note that for serious adverse events and contraindicating adverse events, for both studies shock-like reaction was included.

This slide reviews the numbers of selected serious and contraindicating adverse events from Trial I by a vaccine group and the time intervals post-vaccination of their occurrence. The numbers represent events reported following all three doses. Rates of events were calculated and test of significance performed. And for temperature greater or equal to 40 degrees, crying for three or more hours, and marked local reactions with general symptoms, those reactions occurred at significantly higher rates in the whole cell arm as compared to the CPDT group.

There were six episodes of hypotonic hyper-responsive events reported from Trial I. Five of these were in the whole cell arm and one was in the CPDT arm. This did not represent a significant

difference in rate between the two groups. Rates of convulsions, which included suspected seizures, was not significantly different among the vaccine groups. There was on additional seizure from the entire data base of CPDT that was judged to be related to vaccine and which occurred in the U.S. Bridging Study, and I will be reviewing that event a little bit later.

There were no cases of generalized cyanosis in the CPDT arm, and there were no deaths in the CPDT group. And there were no deaths in any of the studies with CPDT that were submitted for support of the license application. Under the other category, there were three cases of apnea in the CPDT arm. One on day 3 and one on day 8 post-dose one, and one day post-dose two. There was on petechial rash four days post-dose two, a case of Lee's disease on 26 days post-dose one, and Kawasaki's disease 34 days post-dose one.

Hospitalization records from all children enrolled in Trial I reviewed by the clinical coordinating group for the study, and children were grouped by primary diagnosis. The following table was constructed by FDA from line listings of all hospitalization diagnoses for all subjects. The rates of hospitalizations were similar among vaccine groups.

This slide lists selected serious and contraindicating adverse events from Trial II. There were 15 deaths within 60 days of vaccination in the studies, and two of them were in the hybrid or HCPDT group. Both of them were due to SIDS. One occurred 28 days post-dose one and one 45 days post-dose two. Throughout the entire study period, that is from September of 1993 until October of 1996, there were 49 deaths, 10 in the hybrid group. And other than the two cases of SIDS that I have already mentioned, there was one sudden death 175 days post dose-three. The other deaths were all caused by trauma, malignancy or congenitally acquired illnesses. In other trials of the hybrid vaccine, there were two additional cases of SIDS, both in the phase IIC study, which is not being presented today, one 20 days post-dose one and one 6 days post-dose one.

There were 25 seizures that occurred within 72 hours of vaccination in the study, 13 in the whole cell arm and 4 in the hybrid group. The rate of seizure within three days of vaccination was significantly higher in the whole cell arm as compared to the hybrid group.

Temperature greater than 40.5 degrees Centigrade was reported as a significantly higher rate

in the whole cell arm as compared to the hybrid group. There were 101 episodes of HHE reported between 9/93 and August of 1995, when the safety data base was locked for the pre-planned analysis of safety. The rates of HHE in the DTaP groups, as has already been mentioned today, was higher than had been previously reported in other studies with acellular pertussis vaccines. All episodes in this study occurred within 24 hours -- in the hybrid group occurred within 24 hours of vaccination. 20 of the 29 lasted less than 60 minutes, and only one lasted for more than two hours. 14 of the infants received no care, 7 were hospitalized and the others were evaluated and treated at outpatient clinics or emergency rooms.

100 of the 101 subjects who experienced an HHE episode were evaluated at the age of 18 months of age. They underwent a routine exam performed on all children of that age, which is designed to evaluate motor and cognitive development. The evaluation consists of a few simple tests and is designed to evaluate extensive developmental abnormalities. The result of the tests for those 100 subjects and for a reference population taken from one of the child health centers in Sweden are listed here. All children who had an HHE were classified as showing

normal development by the investigators as measured by the test. The one child who was not evaluated had moved outside the country but was reported to have shown a normal development as well.

The technical report, which was written by the investigators offered several explanations for the high rate of HHE in Trial II. One was the increased use of concomitant vaccination with hemophilus B conjugate vaccine. In Trial I, as I will be reviewing later under the section of concurrent immunization, IPV was given starting with the second dose of vaccine and given to about two-thirds of subjects. The hemophilus B conjugate vaccine was introduced while the trial was ongoing and approximately one-third of the subjects received it with dose 2 and 3. In a post-hoc analysis in which children who had received concurrent immunizations with dose 2 and 3 were compared to those who did not. Rates of systemic adverse events were higher for those children in Trial I who had received concurrent immunizations. In Trial II, almost all children received concurrent immunization with IPV and hemophilus B vaccine, at least those who got it at the 3, 5 and 12 month schedule. And the investigators postulated that perhaps the increased use of concurrent immunization

also resulted in the higher rate of HHE.

Another possible explanation put forth in the technical report was a variation in pain. And this, the reasoning behind that was that in an earlier study in which the single component vaccine licensed in the U.S., Certiva, was studied. The vaccine and the DT control vaccine had been given subcutaneously. There were no HHE episodes reported from that study and reports of pain from the group that received the DT arm were lower than historical comparisons. However, for both Trial I and Trial II, which are the studies under discussion today, all immunizations were given intramuscularly.

The investigators noted that there was a variable case definition. The technical reported noted that HHE is not a specific disorder but a clinical syndrome made up of a constellation of symptoms and the classification of an event as HHE is subjective. In Trial I, the case definition was not prospectively defined. But information provided to the FDA, the definition included presence of pallor, lack of muscle tone, and hyporesponsiveness for Trial I. In Trial II, the definition was prospectively defined as a condition in which the child had loss of muscle tone or diminished or absent responses to stimulation. The

definition did not include pallor. However, review of the case report forms indicates that 21 or 22 of the 29 subjects in the hybrid did experience pallor. In three or four, their color was not noted and in two or three, the subject was not pale.

In a reply to a March 2000 CBER letter, APL indicated that they had contacted Dr. Olin, the principle investigator for these studies, and he suggested that the difference in rates observed in Trial I and Trial II was due to better education of study personnel and parents, and therefore a possible over-reporting of HHE in Trial II. However, it must be noted that there was a much more active safety monitoring plan in place for Trial I than there had been for Trial II.

So I would like to review the incidence of HHE in clinical trials with DTaP and then follow it with a review of HHE from all clinical trials with the classic and hybrid formulations. The next two slides are taken and constructed from a publication by Heijbel, et all, in Developments of Biological Standards from 1997, in which the incidence of HHE from eight pertussis vaccine trials were compared. I am going to be going over the studies in which acellular vaccines which are currently licensed in the

U.S. were studied as well as the trials for the two vaccines that are under consideration today.

The publication included a table in which the study, the number of HHE episodes per vaccine group, the number of children enrolled in the vaccine group, and the incidence of HHE per 100,000 was calculated. And that is the information that I have reproduced.

The first study is a study in which the three-component SmithKline vaccine licensed in the U.S. as Infanrix was studied. And there was one HHE episode per 22,500, for an incidence of four per 100,000. A German study in which the four-component vaccine manufactured by Lederle and licensed in the U.S. as Acel-Immune was studied. There were no episodes of HHE in any of the arms.

In a Swedish efficacy study which I mentioned a little bit earlier in which the single component acellular vaccine licensed in the U.S. as Certiva was studied. There were also no episodes of HHE. And in a German study in which the two component acellular pertussis vaccine licensed by Aventis as Tripedia in the U.S., there were two episodes in 12,700, for an incidence of 16.

In Trial I, there was one episode in the

CPDT arm, as already mentioned, for an incidence of 39 per 100,000. In the whole cell arm, there were 5 in that study for an incidence of 250. In an Italian study in which Infanrix, the three-component SmithKline vaccine, was studied, there were no HHE's in that arm. However, of note, there were two HHE episodes in the DT control arm. out of 1,600 subjects, for an incidence of 121. The whole cell vaccine studied in that arm was the same as the one studied in Trial I, and there were 192 episodes per 100,000. And the incidence for the various vaccine groups in Trial II are listed on this slide. The whole cell arm had the highest incidence of 164. And of the acellular vaccines, HCPDT had the highest incidence with 140. But this was not significantly different from the other vaccine groups.

So looking at the overall incidence of HHE from all studies with CPDT and the hybrid vaccine, there was only the one reported episode of HHE from all clinical trials submitted in support of the application. For the infant series, the calculated rate of the rate was 26 per 100,000. And if all doses are included, the incidence is 25. By that I mean the fourth dose as well as the infant series. The incidence is 25. For the hybrid vaccine, there are a

total of 33 episodes of HHE. 29 of these came from the Sweden II Trial. The overall incidence for the infant series is 138, and if all doses are included, it is 141 per 100,000 children. I have also listed on this slide the incidence per 100,000 doses because that information was available for these vaccines.

If one excludes Sweden Trial II and looks only at the incidence of HHE following receipt of hybrid from the other clinical trials that were submitted in support of this application, that is from phase II studies, there were four cases of HHE among 2,367 infants and 8,047 doses. The incidence in the infant series in those studies then is 127 per 100,000 children and 151 per 100,000 children.

So I think that the conclusions that one can draw from the information is that the rates of HHE in clinical trials with pertussis vaccines is variable. For most studies but not all, the rates in the acellular arm -- excuse me, in the whole cell arm, the rates were high. And for studies with the hybrid vaccine, the rate was high in both Sweden Trial II and in other supporting studies.

I would now like to review the data on compatibility of concurrent immunizations. And with regard to these data, CBER is asking the committee to

discuss the adequacy of the data to support 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.

This table provides the size of the safety data base for concurrent immunization from U.S. and North American studies. In the next slide, I will review the data from Sweden Trial I. I have broken out in the infant series the U.S. Bridging Study because that is the only study from which immunogenicity data are available with concurrent immunization.

For the fourth dose, the sponsor did present some data on the use of hemophilus B -- immunogenicity data on the use of hemophilus B when given concurrently with CPDT. Those data will not be presented by FDA as they were felt to be difficult to interpret. There were two groups that were studied. The numbers were small, 21 and 29. While the GMTs were higher in the group that received the vaccines on the same day post-vaccination, they were higher pre-vaccination. Those children were enrolled from the IIC study in which hemophilus B conjugate vaccine was supposed to be given with the infant series, although

not all children got it and the study reports that the fourth dose did not identify definitively that all children had received the infant series.

As noted earlier in the discussion of HHE, the rates of systemic adverse events in Sweden Trial I in a post-hoc analysis when concurrent immunizations were given with dose two and three were noted by Olin, et al., in a publication in the International Journal of Infectious Disease in 1997 were noted to be higher. This is illustrated on this slide. This was especially true when both IPV and Hib were given together. The same observation was noted for dose three.

Concurrent immunizations were given in the U.S. Bridging Study and safety was monitored by the use of diary cards within the first 72 hours. And I have listed the rates of systemic adverse events from this study following the three doses. Most children in the study received hemophilus B conjugate vaccine, OPV and 102 out of the 321 received hepatitis B at a 0, 2 and 6 month schedule. I would just like to note that systemic reactions did not increase with successive doses in this study.

As I noted earlier, all available immunogenicity data on concurrent immunization with CPDT were obtained from the U.S. Bridging Study. There

was no group of children that was to receive these vaccines at separate times to provide comparison of immunogenicity results if vaccines were not given concurrently.

Vaccines were to be given according to the local standard of care. So the vaccine manufacturer was not pre-specified. But FDA asked that for the analyses of hemophilus B conjugate vaccine responses that only subjects who had received PRPT be included, and who had received it at 2, 4 and 6 months of age. And almost all children from whom sera was available met those criteria. The GMCs -- the results were provided by CPDT lot and I listed on the slides that the GMCs between the two were comparable, the rates and the percentage, achieving a level of greater than or equal to .15 micrograms and 1 microgram are listed.

For the analysis of polio virus responses, only those children who received OPV at 2, 4 and 6 months of age and from whom sera were available were included and the results are expressed as percent achieving a neutralizing antibody titer of greater than or equal to 1 to 8 post dose-three.

For the analysis of hepatitis B responses, again only those children who received vaccine at 0, 2 and 6 months of age are included. The numbers in

each group are small. And as I said earlier, the manufacturer was not pre-specified, so not all children received the same hepatitis B vaccine. Of note, for the information on concurrent immunization, there are no data on administration of CPDT with varicella, MMR and the recently licensed pneumococcal conjugate vaccine, Prevnar.

So while in some instances the numbers are small, the antibody responses for those vaccines where information is available are within the realm of what has been seen historically as well as the percent of children receiving zero protection. That concludes my presentation. Thank you.

DR. GRIFFIN: Okay. Questions for Dr. Geber? Dr. Kohl?

DR. KOHL: Are there any data with IPV? OPV is kind of obsolete at this point.

DR. GEBER: There are no immunogenicity data. There was the safety data from Trial I.

DR. FAGGETT: That leads into my question. When were the clinical trials conducted? Was this 1991/1992? I see reports in 1997, but when were the clinical trials and what were the demographics of the subjects that were studied?

DR. GEBER: Okay. So most of the studies

were conducted in Canada and the vast majority of the subjects were Caucasian. Excuse me, let me -- that is incorrect. Many of the studies were conducted in Canada. And in Canada, only the age and the sex is recorded. We specifically asked for ethnicity and that was not provided. For the U.S. Bridging Study, the majority -- and I believe -- I don't have the exact numbers at my fingertips here, but it is in the briefing document. The majority of children, I believe it was over 90 percent, were Caucasian. But if somebody has got the briefing document in front of them.

DR. FAGGETT: And the year of the trial was 1991/1992?

DR. GEBER: The years of the studies varied, but they were for the most part in the early 1990's.

DR. FAGGETT: So prior to IPV.

DR. GEBER: Prior to IPV. And that was true also for the U.S. Bridging Study. It was initiated prior to the switch to IPV.

DR. FAGGETT: Thanks.

DR. LIVENGOOD: Could you sort of pull out -- because there were several different numbers -- how many in terms of the safety data base there were -- at

different points 637, 526 and 301 participants. I mean, what is the safety data base? What is the n in that as far as you can see? And a little bit with the concomitant immunizations, where there really seems to be very sparse data available.

DR. GEBER: Okay. So the 637 are the total number of children who received a fourth dose of CPDT in clinical trials submitted to support licensure. Of those 637, 526 had received an infant series of CPDT. So that is 111 had received whole cell in the infant series. For the concurrent immunization in North American studies -- sorry, I am trying to get to that table here -- I believe there were 505 who received OPV concurrently with CPDT. I think that is the number you may be referring to in the fourth dose, and 135 who received hemophilus B conjugate concurrently with the fourth dose.

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

DR. STEPHENS: Two clarifications. In the studies with the hybrid vaccine, other than the Swedish II study, you suggested or indicated that there is a higher rate of HHE in those studies as well, is that correct?

DR. GEBER: Well, you know, it is a

difficult statement to make. The data are what the data are. The rates are very variable. I think that what we wanted to bring to the committee's attention is that of the 2,800, I believe, children or 2,300 children, there were an additional four cases of HHE from the phase II studies. So even taking the children outside of Sweden II, the rates of HHE were high in that relatively small or smaller sample size. There was 4 per 2,800 I believe it was.

DR. STEPHENS: The second point is you had mentioned that there is a -- that one theory is that the Hib conjugate was potentially a factor. Can you comment on that?

DR. GEBER: Well, I am not sure that any of the explanations really are explanations. They are explanations -- the first three were put forth at the time that the technical report was written by the investigators. And it is true that an increased rate in other systemic reactions were seen when both IPV and hemophilus B were given. But I don't think that there are any data that link rates of other adverse reactions to rates of HHE. So I guess that this is not an FDA explanation, but one that we felt was put out by the investigators and that we would bring to your attention. I am not sure that it holds in other

studies or that that argument has been made.

DR. GRIFFIN: Dr. Kohl?

DR. KOHL: There is an attempt to extrapolate from very small numbers of rare events in the HHE tables. And I guess I need Tom Fleming to help me with that. Tom, if you have a rate of 0 in 17,000 cases, can you say that is zero versus 1, et cetera? What I am saying is I don't have any trust in those numbers or at least in most of them. Yes? No? Say something.

DR. FLEMING: It's an important question. I think specifically how many people do you have to see in order to have a reliable sense of what the rate is of rare events. I mean certainly one of the major advantages that I see for studies such as the Sweden I and Sweden II Trial is it gives us a very substantial data base for being able to get at events that are less frequent than one in 1,000. Basically we would have in the Sweden II Trial very high power of picking up events that are at a rare occurrence level of one in 1,000, and possibly even one to 5,000. It is essentially at that level that we are powered to pick up events with high probability.

DR. KOHL: But that is not the case of the other studies, is it? Like the Sweden I study had

2,500 in each arm.

DR. FLEMING: It is much more on the order of 1 in 200 or 1 in 500 would be picked up with high probability.

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

DR. ESTES: I have a question about the change in the definition of HHE between the two -- Sweden I and Sweden II studies. Even if you change the definition, is there any question that the changing of that is now reporting something that is not correct? So people may become aware of something that has been there all along and they might have missed it earlier. But is it over-reporting? I mean, we have sort of had this discussion that this is over-reporting. But in fact, if it is a real thing, it is really just a recognition that it existed all along.

DR. GEBER: I think we have had some indication from the sponsor who has been in contact with the principle investigator that study personnel in Trial II and therefore parents, perhaps, were more aware of the event. I think there were some differences in the case definition. In one instance it was more stringent perhaps for Trial I because it included pallor. But in Trial II, it was more

stringent because the child had to not respond to stimulation. So I think the other thing, though, that needs to be taken into consideration is the monitoring plan for both studies. And I think that what we are left with is I am not sure that we know the reason for the higher rates of HHE in Trial II. I don't think we have a definitive answer for why it was. We have some theories or some suggestions.

DR. GRIFFIN: Yes, Dr. Livengood?

DR. LIVENGOOD: I think I would agree with you. The word over-reporting is misused here. I would -- it is very likely that the increased stimulation increased your reporting fraction, if you will, and you are capturing a much larger proportion of events than you were when you don't stimulate. That is a basic surveillance concept. But over-reporting would mean that people are reporting things that aren't HHE's, and that is not what I think is really meant here. But the extent to which the fraction went from 10 percent to 60 percent, is that -- we can't really say. But I don't -- I have a problem with calling it over-reporting as well.

DR. FAGGETT: But, John, would you say it is more accurate reporting then?

DR. LIVENGOOD: It is more reporting.

DR. GEBER: In Trial I, the 14-day post-vaccination phone call, there was a question of did your child experience a shock-like episode. So it was in a sense solicited for, but perhaps not specifically.

DR. GRIFFIN: Yes, Dr. Diaz.

DR. DIAZ: I think I know the answer already, but I am going to ask anyway. Are there any other countries in which there are -- where you have this vaccine licensed where you have post-licensure information about serious adverse events for which there are data bases in those countries that are population based that could be helpful in adding more information?

DR. FAHIM: As mentioned previously, this vaccine is licensed and the only vaccine used in Canada in the HCPDT formulation but in combination with IPV and Hib. That is the vaccine -- the standard of care in Canada for all children in Canada. And, yes, we do have information about that -- about the -- really it is relevant to what was used earlier, which is the whole cell vaccine combination. And now with the acellular vaccine, we have information about that. It is really up to the FDA whether you would like to see this data or not. It is not part of the file. That

is why we have to ask the FDA for it.

DR. GEBER: I guess the caveat that would be added is that we have not reviewed the data. And so we --

DR. GRIFFIN: Right. And so we can't introduce it into this discussion. All right. Other questions? If not, lunch. And then we are back -- we are going to try to stay on schedule. So we are going to get 50 minutes for lunch. So be back at 1:50. Thanks.

(Whereupon, at 12:58 p.m., the meeting was adjourned for lunch, to reconvene this same day at 1:50 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1:50 p.m.

DR. GRIFFIN: We are going to begin the afternoon session with an answer to Dr. Diaz's question, which is to see what the data are like from monitoring of the Canadian experience with reference to HHE. And that is going to be presented by Dr. Elaine Mills.

DR. MILLS: Thank you. My name is Elaine Mills from Aventis Pasteur. The Canadian experience with the hybrid combination vaccine of HCPDT-IPV-PRP-T began in 1997. Almost the whole country had switched over from a whole cell combination vaccine to an acellular combination vaccine within the first six months. So what we are talking about is the standard of care in Canada.

There are several surveillance systems, and I will describe one, because it is a population-based system. And this was -- this is data, first of all, provided by Dr. John Waters, who is the Provincial Health Officer of the Alberta Department of Health and Wellness. Even though this data is not published, Dr. Waters gave us this information and is allowing us to share it with you.

What I want to mention, first of all, is

that the surveillance -- the data that I am going to present was from a surveillance system that was well established before 1997. So they had accumulated a lot of information on vaccine safety prior to the time when there was a switch.

Just a few points about the system. One is that all childhood immunizations are given by public health nurses. And these public health nurses are trained in immunization policies and practices. They counsel parents about adverse reactions and urge them to report adverse events. The public health nurses are required to question parents at each clinic visit concerning adverse events of prior immunizations. And the adverse events are used in the national vaccine adverse events evaluation report. They use the same report form as everybody else in the country does for passive reporting of adverse reactions.

There is coming into the national system a much higher proportion of reports coming from Alberta than from other provinces, and Dr. Waters likes to call this a stimulated passive surveillance system.

With that background and because we are talking about HHEs, this is the definition that has been used in the Canadian reporting system since 1987.

So this is standard reporting. And the definition of HHE is decreased or loss of muscle tone and pallor or cyanosis and decreased level of consciousness or cardiovascular or respiratory arrest. So that is the definition.

These are the data that were collected between 1996 and 1998 in this system. And it was for 18 months of data using whole cell, January 1996 to June 1997, and 264,000 doses were given during that period of time. And acellular vaccine came on board July 1, 1997. And because of their system, they were able to switch almost immediately to the acellular combination vaccine. Therefore, the data then are for the next 18 months, July 1997 to December 1998, where there were 250,000 some doses that were given. This shows the rate per 100,000 doses, whole cell in green and acellular vaccine in orange. Now you can see they were obviously collecting the adverse events that had been associated with whole cell pertussis vaccine. So these are the selected adverse events that are presented here -- fever, HHE, crying, severe local and moderate local reactions.

HHE's are given for -- the rates are given for dose 1, 2 and 3, because all but one HHE occurred in the first three doses. And I will show you the

data by dose as well. As you can see, in the 18 months, the rate during the first 18 months with whole cell was 116 per 100,000 doses. And following the introduction of acellular vaccines, it was about 24 per 100,000 doses. Now these children, if they received -- right after July 1, if they received an acellular vaccine, whether they had received one or two doses of whole cell previously, they were counted now in the acellular vaccine group. So for the first several months then, there was a mixed schedule. They were started to receive acellulars, but they may have previously received whole cell. And then there was a complete switch.

So these are the rates for these severe adverse reactions. There was an 80 percent decrease in the HHE's over that 18 months. And these were the rates per dose. As you can see, the vast majority of them in fact were associated with whole cell vaccine, and there were a few that were associated -- in fact, in this particular data base, there were none of the fourth dose. They were all in the first of the second dose. I think I will stop here, because that was what the question was.

DR. GRIFFIN: Right. Okay. Are there any questions related to this? Yes, Dr. Katz.

DR. KATZ: Elaine, my assumption is all of these children recovered. There were no fatalities, is that correct?

DR. MILLS: That is correct.

DR. KATZ: Thank you.

DR. MILLS: In fact, you mean of the follow-up of those --

DR. KATZ: The HHE's.

DR. MILLS: Yes, they were all well.

DR. GRIFFIN: Okay. Other questions? I have one correction that I forgot to mention at the beginning of the session that the company has called to my attention, which is on page 64 of your book. And that is relevant to this current discussion. The line that says only two HHE cases were observed in 69,525 doses, that is the wrong denominator. That denominator is actually 6,550 doses. So for the record, we wanted to make sure that was corrected.

Okay, now we are going to move into open session -- open public hearing, excuse me. We have been in open session this whole time. We are now in open public hearing. You can tell I am a new person at this. And our first speaker is Dr. Stanley Plotkin. And you are asked to announce your affiliation.

DR. PLOTKIN: Yes, my name is Stanley

Plotkin, and I am a consultant to Aventis Pasteur. I just want to make several comments on the prior discussion. I have been interested in this vaccine for ever since I heard about it. Primarily because from the theoretical point of view, this was an attempt to reconstruct with acellular components, that is with individual components, and efficacious whole cell vaccine. And that is to include all of the factors which were thought to be protective factors. And indeed I think the Canadian investigators succeeded in doing that.

We have heard a great deal of discussion about correlates of efficacy, and I won't go through the tedious repetition about the multiplicity of factors which do seem to correlate with protection. But again, the point was to introduce redundancy into the vaccine. That is to say to have as many protective factors as could be justified scientifically.

The ultimate test, of course, is efficacy in the field. And we have heard that before. The trials that were organized in Sweden and in Italy were, as you know, financed by the United States, and financed in an effort to bring efficacious and safe pertussis vaccines into the United States. Therefore, it seems a little strange to me to hear some doubts

expressed about the vaccine which appeared to have been the most efficacious of all of the vaccines tested.

If my memory serves, and I can be corrected if I am wrong, the SmithKline tri-component vaccine also showed some differences in pertactin antibody levels, that is, between the studies done overseas and the studies done in the United States. However, the vaccine was licensed, properly so, because of the efficacy data from Germany and from Italy. So I think one should be consistent.

I would also like to point out some things about the second Swedish study, of which we have heard a great deal today. The point of introducing the data, or one of the major points certainly, was to show that the pertactin antibody levels were not necessarily relevant to the protection produced by the vaccine. Because as was shown, the pertactin antibody levels in Sweden II were significantly lower than titers in Sweden I. And yet, the vaccine appeared to be efficacious, although some doubt was introduced about that at this meeting. It is true -- and I am sorry Dr. Fleming is not here -- but it is true that the confidence limits of the primary analysis were over 1.5, although the point estimate indicated high

efficacy. However, I think you have to look at the totality of the data. You have, I think, probably in your pre-reads the paper that recounts Sweden II. And I call your attention to the fact that if you look at Table 2, which is the --

DR. GRIFFIN: Do you want to say what page you are on?

DR. PLOTKIN: Sorry?

DR. GRIFFIN: What page so people can follow along.

DR. PLOTKIN: Well, I don't know what page it is in your handout. It is page --

DR. GRIFFIN: Does your handout look like this handout?

DR. PLOTKIN: Yes.

DR. GRIFFIN: Okay. I think we are on the same page so to speak.

DR. PLOTKIN: It is page 1573 of the original document. But that is -- it is towards the end of this packet.

DR. GRIFFIN: Okay. So it is the paper at the back, page 1573.

DR. PLOTKIN: Yes.

DR. GRIFFIN: Okay.

DR. PLOTKIN: So what that shows is that

the criterion for diagnosis of pertussis was culture. In the absence of serologic data. And, therefore, there were relatively few cases in that primary analysis of pertussis. This accounts for the weak power. If, however, you look at the Table 3, which compares the vaccines to the SmithKline two-component vaccine, one sees that the three-component and the five-component and the whole cell were all significantly more efficacious. Now it should be remembered that that two-component vaccine was not without efficacy. It was about 60 percent efficacious. So it is not comparing to placebo. It is in fact a rather tough test, and yet efficacy was shown.

And finally, if you look at Table 4, in which the authors tried to make up for the deficiency in diagnosis -- that is, for the absence of serologic criteria -- they asked parents to tell them whether the child had an illness diagnosed as pertussis during the study period. And then they did a statistical analysis. Now since this was still a blinded study, I think we have to take these data seriously. And especially since the bias, if any, was against the vaccine by taking into account non-pertussis cases. And yet we see that for certain diagnosis of whooping cough in Table 4, that the efficacy of the five-

component vaccine was -- compared to the whole cell was 1.12, with confidence limits of .9 to 1.4, indicating that indeed under this analysis that the five-component vaccine was equal to a highly effective whole cell vaccine.

Finally, I would like to introduce a point which is irrelevant in a sense to the considerations of the committee, but is certainly not irrelevant to those of us who are interested in public health. And that is that this vaccine, this acellular pertussis vaccine, is the only acellular pertussis vaccine which does not show an interference with hemophilus influenza. Consequently, when combinations of this vaccine are introduced, it will be possible to reduce the number of injections being given during the infant pediatric schedule, which is something I think we would all like to achieve. And as I say, this is perhaps not relevant to the isolated consideration of this vaccine, but it is an important public health issue. And I certainly believe that the vaccine had fulfilled the criteria for both safety and efficacy. Thank you.

DR. GRIFFIN: Thank you. The second and only other that we know of speaker in the open public hearing is Dr. Michel DeWilde.

DR. DEWILDE: Good afternoon. My name is indeed Michel DeWilde. I am with Aventis Pasteur. A little bit like Michael Decker, I would not have imagined ten years ago that I would be sitting here today. The reasons for that are totally different, however. Ten years ago, I was with SmithKline Beecham and hence don't review the development of Infanrix.

So without breaking any intellectual confidential, I would just like to testify to the committee that each vaccine has to be taken on its own merit. And even so we keep saying that we should not keep comparing two vaccines of similar comparison. Again, we should be very careful when we do that.

A given antigen in two different vaccines is not necessarily the same. So if the antigen is purified and extracted or is the antigen detoxified the case being, and the amount of the antigen is different from one vaccine to another. So we should be very careful in extrapolating from comparisons that we should not do.

Another point I want to make is that indeed as we were conceiving the vaccine, we were aware at that time of all the data for which to choose in terms of trying to pick what would be protective antigens. Included in those data were those that Dr.

Fahim earlier this morning pointed out and which are those epidemics that occurred in the time of the whole cell vaccine due to strains containing fimbriate type that were not present in the whole cell vaccine. Pointing and making very strong evidence that fimbriae is a key and definitely a protective antigen. So it was to reiterate Dr. Plotkin's point on the unique polyvariancy of CPDT, which does contain those fimbriae in an amount that until recently I thought was not technically feasible, by the way, and I have great admiration for Raafat for doing that.

So I just wanted to restress to the committee to look at this vaccine in the entirety in terms of its composition and what each of its components can contribute to efficacy. Thank you.

DR. GRIFFIN: Thank you. Is there anyone else who wishes to speak in the open public hearing? If not, we will move to the committee discussion, which can include a question.

DR. FAGGETT: Okay. I had a question for Dr. Plotkin. He mentioned the fact that this vaccine had no interference with Hib. Were there some data available for that somewhere?

DR. PLOTKIN: Dr. Faggett, there are data, yes. They are not on the table here because the only

vaccine that is being considered here is the DTaP. However, there are data, mainly from Canada, to show that you can combine in the same syringe hemophilus influenza and this particular acellular pertussis vaccine without seeing a reduction in the titers of antibody to PRP.

DR. FAGGETT: And you have also experience with giving the vaccine to patients who had Hib? Do you have any of that experience clinically of patients -- concomitant immunization with Hib in the acellular in Canada?

DR. PLOTKIN: Oh, yes. Yes.

DR. FAGGETT: Okay.

DR. GRIFFIN: Okay. Any other questions that were specifically directed at the speakers? If not, I think we are going to now move into the committee -- oh, excuse me, Dr. Goldberg.

DR. GOLDBERG: One other question for the Aventis. When you did the Bridging Study and you did the -- when you compared the titers from before -- pre and post titers, you were missing about 20 percent of the samples. Do you have any idea what the reasons for that were and are there any potential sources of bias that you have identified that might influence the outcome?

DR. GRIFFIN: I think the Bridging Study were not all the sera were available for comparisons.

DR. FAHIM: Right. Where it is about 70 percent or so of the sera were available. We actually looked at that to see the distribution of sera and the immune response, and this was a very good representative sample of the whole. There was no bias in it at all, and this is obviously, as you can imagine, one of the questions the FDA asked us originally anyway, and they satisfied themselves that there was no bias in it.

DR. GOLDBERG: Would you have that data to show us by any chance?

DR. FAHIM: Yes, we do.

DR. GOLDBERG: Thank you.

DR. FAHIM: If you can give us just a few minutes to sort through it. Meanwhile, maybe if you wanted to continue.

DR. GRIFFIN: Right, we can -- all right. I think the way we should structure this discussion is to begin with -- since we are going to eventually then go through and be addressing the specific questions that the FDA has posed to perhaps go through in that sort of order so that we can structure this discussion a little. And then we will -- there will be two of

these questions for which there will be a vote, and that will be question 1A, are the data adequate to support the efficacy of the acellular pertussis component when administered in infants and children in the USA as a four-dose series? And then if not, what additional information should be requested? And then also question 2, are the data adequate to support the safety of CPDT? Please specifically address both the infant series and the fourth dose data. I guess it is my inclination to sort of start with the safety data, because I think in some ways that is a little easier discussion. And then to go to the question 1 on the efficacy data. Is that okay with everybody? Okay. So if we start with questions, discussions, et cetera, relevant to the safety issues. Okay, we are ready with the data that are relevant to efficacy.

DR. GEBER: The question that was just asked, the response was reviewed by FDA regarding bias in selection. And the results are on -- I know it was a lengthy document, but the clinical trial summary, the draft on A-21. We did ask the company to look at whether there was any bias in excluding 20 percent of the samples. There was some evidence that perhaps that the -- and it is in the paragraph underneath the third table, the results. There was some evidence that

in omitting the 20 percent or so samples, that perhaps the differences between lot 006 and 009 was larger in the pre-validated assay or would have been than resulted in the reassay. In other words, there was some difference between the two lots, 006 and 009, in the GMCs that were presented. That might have been somewhat larger had all samples been included. But 006 would have looked perhaps a little bit more like Sweden I and 009 a little bit less, but it was not dramatic.

DR. FAHIM: So these are the reverse cumulative frequency distributions here. And you can see it is not as clear, but this is U.S. lot 6, U.S. lot 9 -- U.S. lot 6 not tested and U.S. lot 6 tested. I apologize for the quality of the overhead. I guess the point is that they are -- for the PT, FHA and fimbriae in the 69K, they more or less overlap with the exception here of the 69K. Maybe that is a minor difference between them.

DR. GRIFFIN: Thank you. Okay, now committee discussion on the question of safety. Any other questions or any other points that need to be brought up or that you want to make that haven't already been made? Yes, Dr. Huang?

DR. HUANG: I really just need some