clarification here. Because we are deciding between three doses and four doses.

DR. GRIFFIN: No. Well, I think -- oh, you mean for the --

DR. HUANG: For safety. Question number 2.

DR. GRIFFIN: Right.

DR. HUANG: Please specifically address both the infant series and the fourth dose data.

DR. GRIFFIN: Right.

DR. HUANG: And I realize that what we are seeing, much of the result -- most of the patients only received three doses and that a small subset of them got a booster or fourth dose. And we are judging the fourth dose based on that?

DR. GRIFFIN: Right. Dr. Geber, I don't know if you want to elaborate at all on exactly the quality of the data.

DR. GEBER: Yes, I think that is correct. It is a considerably smaller sample size for the fourth dose than for the infant series. In fairness, other acellular pertussis applications that have come before this committee -- and I don't have the exact numbers in front of me -- but the fourth dose data have generally been somewhat smaller than the infant

series. I can't provide you exact numbers to compare as to how much smaller this might be or whatever. But it is --

DR. KOHL: Remind us what numbers we are talking about for the fourth dose.

DR. GEBER: Okay. For the fourth dose, it is 637 infants. 526 of those received four consecutive doses of CPDT. The other 111 had received whole cell in the infant series.

DR. HUANG: And the FDA has no problems with that in general?

DR. GEBER: I think that we invite your comment.

DR. GRIFFIN: Okay. Yes, Dr. Livengood?

DR. LIVENGOOD: I personally think that is a very small number of people. We recently have become more aware of this whole limb swelling, and we can't really judge what the possibility of that is. I mean, we are aware that with the increasing number of doses, the adverse events for acellular vaccines go up. So the fourth dose, in fact, is sort of more critical to us than perhaps it would have been when we were licensing the first of these and we didn't notice yet at that point that the trend was going to be as strong for the fourth dose or subsequently for fifth doses

that we have noticed. And certainly with just 500, and I assume that that might be one of the things that Dr. Fleming was going to mention, it is hard to make any estimate about what the rate of really pronounced limb swelling might be with just that number of observations, even though it wasn't really noted here.

DR. GRIFFIN: Dr. Fleming?

DR. FLEMING: Yes. I think we have some important insight, but I think we are also lacking some important insight for the fourth dose. There is, in fact, potential for increased risk that didn't exist with the three doses. The 637 were in a position to have a reasonable sense of what that increased risk is for the more frequent types of events. For the rare types of events, not suggesting that this would have to be pre-marketing, but if this were approved, it certainly would be important to have surveillance, and it would take 10,000 -- surveillance of about 10,000 to begin to have confidence that you are picking up the serious types of risks that could be occurring with enhanced frequency with the fourth dose. And the other thing that was noted by the FDA is the lack of information on what the even more frequently occurring safety risks might be in the fourth dose when it is administered before 17 months. So those are the two

features that I see that aren't yet flushed out. What the frequent risks would be when the fourth dose is delivered before 17 months, and then what the rare but important risks would be that would be intrinsically higher risks due to the administration of the fourth dose, and that hasn't been studied, even though it has been very carefully studied for the first three doses in Sweden I and Sweden II.

DR. GRIFFIN: I think Dr. Katz is next.

DR. KATZ: I don't know if this is out of order, and again I will only get away with this at one meeting I realize. But as a new member, you have sitting in the audience probably the one person in this country who has the most experience with fourth and fifth doses, and that is Dr. Peggy Reynolds sitting behind Dr. Plotkin. Is it fair to ask her for an opinion on this?

DR. GRIFFIN: We can ask her. Dr. Reynolds will be asked to state all of her affiliation.

DR. REYNOLDS: I conduct or am soon to conduct vaccine trials sponsored by Merck, Aventis Pasteur, Wythe and SmithKline Beecham. And I chair a safety monitoring board for Aventis Pasteur. I am not sure what the question is. But let me describe the

data we do know very briefly. When we became aware that following the fourth dose -- the fourth consecutive dose of DTaP, I with my colleagues did a retrospective survey of the children enrolled in the Multi-Center Acellular Pertussis Trial. There were about 2,300 children. 150 of those had the same -- four doses of the same DTaP. Entire thigh swelling was seen with nine of the twelve different vaccines, and those nine different vaccines contained PT alone, PT/FHA, three-component, four-component. It was clearly a problem with the class of vaccines and not any individual vaccine. The overall rate of swelling reactions was 2 out of this 1,015 or about 2 percent. It really was impossible to adequately compare one vaccine rate to another because the numbers are really small. You vary from per vaccine zero to I believe four cases. And so you get a sense that there may be some difference, but it is retrospective. It is not valid.

The other thing one needs to know is that the way we got these data was by examining all the comment section of the parents' diary card. We didn't expect the reaction, just like these people didn't, so we didn't prospectively survey for it. So that is not the best way to get data. It may be an under-

estimation.

I can tell you that this -- although I don't remember the exact numbers and I regret I didn't review them before I came. But I can tell you this vaccine was not at the top. As I recall, it was somewhere in-between. The other thing to be aware of is that these reactions in general look worse than they are. Because 40 percent of the kids were judged by their parents to have no pain whatsoever. And so the parents were unconcerned. Only three of the 20 were judged to be in severe pain defined as not wanting to move the extremity. They all resolved by about four days without any sequelae. Did that sort of answer what you wanted to know?

DR. KATZ: Thank you.

DR. GRIFFIN: Thank you. Dr. Myers?

DR. MYERS: Like Dr. Fleming, I am not sure that this is necessarily an issue that needs to be addressed pre-licensure. But in the original studies, there was a racial difference in both pain and fussiness as well as serologic response. I think that needs to be examined, particularly when we are talking about pain.

DR. GRIFFIN: What do you mean by the original study?

DR. MYERS: In the --

DR. GRIFFIN: The Sweden --

DR. MYERS: In the Sweden I.

DR. GRIFFIN: Sweden I. Okay.

DR. MYERS: And I don't think we have heard any data that would allow us to address that issue.

DR. GRIFFIN: Okay. Other comments?

DR. KOHL: Was that Sweden I or the original NIH studies in this country? Is that the pediatric supplement?

DR. MYERS: Yes, the pediatric supplement.

DR. KOHL: Those are the NIH studies, I believe.

DR. GRIFFIN: So it was the NIH studies in the United States?

DR. KOHL: Right, in the early 1990's.

DR. GRIFFIN: All right. The same ones that Dr. Reynolds was talking about. All right, other discussion? I think what I am going to do, since we have two questions that we are going to vote on, is to go ahead and vote on this one, number 2, and go around. And then we will move to the 1A and B questions on the efficacy and then vote on those after that discussion and then move on to the other

questions. Okay. Can we start with you, Dr. Stephens?

DR. MEADE: I am sorry, just a point of clarification. As chair -- you are running the meeting, so that was fine. I was just going back to the comment Dr. Huang made. Again, the way the safety may be viewed differently depending upon how the vote comes on the first question. So, again, I wanted to be sure that you were comfortable with the vote on the safety prior to the discussion of the efficacy. I know the efficacy is a little more difficult. But in terms of the context and the way that the potential responses to safety could depend upon how the efficacy question is viewed. I just wanted you to consider that first.

DR. GRIFFIN: Okay. Discussion? Do you feel it would be more appropriate to -- I mean, I really viewed them as two separate questions. But I am certainly willing to go back to the original plan.

DR. FAGGETT: Diane, I personally like the idea of safety going first. So often it is short-thrift. So as a member of the committee, I would support your recommendation that we discuss safety first.

DR. GRIFFIN: Okay. We don't want to go

against protocol.

DR. MEADE: That is fine.

DR. GRIFFIN: All right, we are going to be allowed to. So we are voting on question number 2, which is the safety, and then also comments from each of the individuals on what -- both on the three dose/four dose issue and on what additional information should be required.

DR. STEPHENS: It is always dangerous to go first.

DR. GRIFFIN: I know.

MS. CHERRY: The question is are the data adequate to support the safety of CPDT for starting.

DR. STEPHENS: I think the data are adequate. The safety issues are comparable to the currently licensed acellular pertussis vaccines. So that is the kind of bottom line. Now I think that there are two points that I think are important. One is the issue of HHE's, which we have discussed at length today, and I think we don't fully appreciate what that syndrome is. But I think that the data do suggest that at least for the classic vaccine that the rates of HHE are not higher. But I still have some reservations about that particular issue. And I think that that deserves some additional study.

The second has to do -- I am reassured to some degree by the Canadian data that was presented, the post-marketing data on safety. I think that was very helpful. I am sorry that wasn't actually submitted to the FDA prior to this meeting. I think the other concerns I have have to do with the fourth dose issue, which I think is not clarified. The numbers, as has been pointed out, are small. And when the doses were given -- the 17-month issue that was raised is also. So I think with those caveats and with those reservations, I think it is comparable to the currently licensed acellular pertussis vaccines from a safety perspective.

DR. GRIFFIN: Okay. Thank you. Dr. Estes?

DR. ESTES: Dr. Stephens has really hit most of the points that I have. I think the -- I am a little concerned about the numbers being small. I think in particular for the fourth dose, I think we need more numbers. I think that the data do suggest that this is a safe vaccine. I am also -- I am not totally convinced that the HHE won't be a little bit higher if there were more numbers to look at. And I think ultimately we are going to need more data from other special groups, perhaps from other minority groups.

DR. GRIFFIN: Thank you. Dr. Katz.

DR. KATZ: I too believe that I would vote affirmatively, yes, on both issues with my caveats being that we continue to enlarge the sample sizes with post-licensure surveillance.

From the issue of safety, I would point out an issue that hasn't even been mentioned today that is certainly prominent in the media, and that is thimerosal. This vaccine has 2-phenoxyethanol and does not have thimerosal, which makes it a safer vaccine from some people's perspective than the licensed vaccines previously.

DR. GRIFFIN: Dr. Huang?

DR. HUANG: I have been noisy enough. So I am not going to repeat what has already been said here. I believe that the -- what has been provided today supports the safety of CPDT. And I go along with what has been said about the third and fourth doses.

DR. GRIFFIN: Dr. Kohl?

DR. KOHL: I concur with the rest of the committee members so far.

DR. GRIFFIN: Thank you. Dr. Manley?

DR. MANLEY: I continue to have concerns about the small size of the sample as well as the

continuing issue that is being raised about the lack of racial differences here, represented even in the small samples. I would concur with the committee on the safety of the -- in the presentation. But I certainly think that we need to give more attention to the numbers and sample size.

DR. GRIFFIN: As a post-marketing -- if it gets to that point?

DR. MANLEY: Well, I haven't gotten to that point.

DR. GRIFFIN: Okay. All right. Dr. Diaz?

DR. DIAZ: I likewise concur with my colleagues and what they have stated in terms of the safety overall and also the concerns that have been raised on a third/fourth dose and a lack of representation of minorities, et cetera. Nonetheless, I do think it is comparable to currently licensed. For post-marketing issues, in terms of surveillance, I think that it is extremely important that we, from a national standpoint, begin to define more solidly definitions, for instance, for HHE and focus on some even more population-based post-marketing surveillance than we currently do have in trying to look at these studies from a much larger perspective. Because as has been pointed out, the rare events are much more

difficult to pick up in some of the smaller studies.

DR. GRIFFIN: Thank you. Ms. Fisher?

MS. FISHER: I really think there needs to be a large trial done in the United States in genetically diverse populations, with particular attention paid to better understanding the biological mechanisms of HHE with this vaccine as well as host factors which could make some children more susceptible. And that there be longer term follow-up of the serious adverse events. And one of the reasons I am concerned about this is that I know that if this vaccine is licensed that the children who get this vaccine are not going to be the ones that were studied in this population unless that is stipulated. But it just seems as if there needs to be more study done in genetically diverse populations.

DR. GRIFFIN: So is that a no vote?

MS. FISHER: That is a no.

DR. GRIFFIN: Dr. Faggett?

DR. FAGGETT: I am -- I would be a lot more comfortable if we did have more data from a more diverse population so we could better anticipate any adverse events. But I think the point that other members have made that we need to look at the fourth dose -- this might be an opportunity to have

additional clinical trials which could be more inclusive. So that we would get what a lot of the committee members are asking for. I would like to abstain at this point in terms of safety.

DR. GRIFFIN: Dr. Goldberg?

DR. GOLDBERG: I would vote yes for safety with the stipulation that a careful post-marketing surveillance program is implemented and put in place.

DR. GRIFFIN: Dr. Fleming?

DR. FLEMING: I think I have a similar sense. I am impressed with the care that was given in the assessment in the Sweden Trial I to providing what I would see to be very encouraging evidence. For me safety is a lot easier issue to address here than efficacy.

DR. GRIFFIN: That is the reason I chose it first.

DR. FLEMING: And I think in particular if we are looking at a relative to the whole cell, that is really where some of the best, most encouraging evidence is coming forward. Specifically to the three dose regimen in the Swedish population, my biggest interest would then be to hope to see an expansion of this safety experience for the four dose regimen. To the extent -- the Alberta data could certainly have

some relevance here, although this is something I am not fully convinced, given that as I understand it, it is a fourth dose following whole cell vaccination. But in any event, I think the FDA should be -- I would recommend that they would seriously consider ensuring that there is adequate safety data gathered for the four dose experience to be able to reasonably address the impact on events such as HHE events, which are more on the order of 1 per 1,000. So we are talking experiences that would require possibly in post-marketing surveillance 10,000 or more.

DR. GRIFFIN: Dr. Myers?

DR. MYERS: I think I agree with most of the previous comments. I think there is clearly adequate safety data for the three dose regimen. I am not certain that there is adequate safety information for the fourth dose. Although the vaccine has been used widely elsewhere in the world. I would agree with the previous two speakers. I think post-marketing evaluations to include much more diverse populations would be critical of both the three dose and the four dose level and active surveillance post-marketing.

DR. GRIFFIN: Yes, Dr. Livengood?

DR. LIVENGOOD: I would agree that the data are adequate to support the safety of this

vaccine given at 2, 4 and 6 months of age. I think the data are marginal at best at 17 to 18 months of age -- 17 to 20 months of age. And non-existent and 15 to 16 months of age. And I would hope that the FDA would address that in terms of the licensure.

I am sensitive to the idea that we are perhaps asking for more fourth dose data than what we did with previous acellular vaccines, but I think that frankly the situation has changed. We have a better understanding of what is going on now with the number of doses going up and the possibility of these whole limb swellings, even if they turn out to not be of particular importance. So I am not as willing to just say, yes, I would support it. Because in the past I supported licensure of vaccines at fourth dose at about this same number of immunized children.

DR. GRIFFIN: Dr. Hewlett?

DR. HEWLETT: Certainly things are getting more complicated with more information as we go along. I think that the data are adequate also. I would like to make a comment about HHE, upon which we are focusing here. It is a very interesting phenomenon and one that in talking to Ms. Fisher before, given the dramatic reduction in local reactions that occurred with acellular vaccines by reducing the endotoxin

concentration and the endotoxin dose by 10 to 100-fold and by eliminating active pertussis toxin, there hasn't been as dramatic a reduction in the HHE as one might have expected. If you look at these data, they are not dramatically decreased -- not 10-fold decreased from the whole cell vaccine. And I think that is something that we need to continue to pay attention to. It certainly is not an issue for which we have an animal model or any good way to address other than in humans, which really comes back to the possibility of follow-up studies.

DR. GRIFFIN: Okay, thank you. And for the record, I would agree that the safety data are adequate for the three doses, but with the new information on fourth dose, I would like to see more data there. All right. Yes, Dr. Kohl?

DR. KOHL: Just one comment. On the post -- in terms of the fourth dose. If it is post-surveillance or if it is pre-licensure, and I am not sure how the committee --

DR. GRIFFIN: Well, I think that in some ways we've got to discuss the efficacy issue before we are talking post-licensure or anything else.

DR. KOHL: No, that is not my point. However it is done, I think it has got to be done

compared to another acellular vaccine. Because we -- as Dr. Reynolds pointed out, we at this point don't have good prospective careful data on what some of these new side effects are. In order to make any sense out of these side effects in a new vaccine, we have to know what the baseline is in some of our currently accepted products.

DR. GRIFFIN: Good point.

DR. GEBER: So -- it may just be me. So am I -- do I understand then -- so we aren't voting on the -- we, not me -- on the fourth dose just yet? Or for the safety --

DR. GRIFFIN: Well, I think there is a consensus on the three doses. But there also appears to me to be a consensus on not thinking there is enough data for the fourth dose. Is that a fair summary? No? Go ahead.

DR. KOHL: I think there is a consensus that there is not enough data. But whether it should be post-licensure or pre-licensure hasn't been settled in the committee's mind, I don't think.

DR. GRIFFIN: Right.

DR. KOHL: I heard some people say post-licensure, which I would agree with.

DR. GRIFFIN: So can we defer that until

we at least discuss the efficacy issue?

DR. GEBER: Sure. I just --

DR. GRIFFIN: Licensure may not be an issue if it is not efficacious.

DR. GEBER: Sure. Absolutely.

DR. GRIFFIN: Then we can -- then maybe we can round out the overall opinion. Okay.

DR. MEADE: I would just like to agree. It is an extremely important clarification on the fourth dose.

DR. GRIFFIN: Okay.

DR. MEADE: Distinguishing pre versus post-marketing.

DR. GRIFFIN: Okay. We will come back to that.

DR. MEADE: That is an important clarification.

DR. GRIFFIN: All right. So we will come back to that part of question 2 after we have discussed question 1 and we have reached hopefully some sort of consensus on efficacy. So now we will begin the discussion on efficacy. And the question that we are addressing is are the data adequate to support the efficacy of the acellular pertussis component of a CPDT when administered to infants and

children in the U.S. as a four dose series? If not, what additional information should be requested? So I will open it up to whoever wants to begin. It seems to me from a person who is coming from outside the pertussis field and who therefore has read the literature in preparation for this meeting plus listened to people that there are two or three different issues that maybe the discussion can help us focus on. One is that this vaccine is being brought to licensure in a little different climate than previous ones were. That the trials outside the United States are necessary. That is the only way you can get efficacy data, because those were the only places you were going to see enough pertussis to be able to know whether it was efficacious or not. That those trials cannot be done in the United States because there is a high degree of immunity to pertussis. Therefore, we will never get efficacy data within the United States. That as a part of moving data from outside the United States to the U.S. population for consideration by the FDA, that the criteria of equivalency has been applied to vaccines, and I think maybe that is part of what needs to be clarified is exactly what is meant by that. Particularly when you are talking about many

components to a vaccine, does every single one have to be equivalent? I think this is not law. My understanding is that this is not written down as code. So that these will become judgment issues for this committee to determine. And in this case, we have a component where there is not equivalency. Where the component -- there is some data to suggest that an immune response to this component is an important part of the efficacy of other vaccines. Is that fair from the people who really know this field? Okay. Now the people who really know the field.

DR. HEWLETT: I think that is a good summary of where we are. There is no doubt in my mind that this is an efficacious vaccine in the Swedish population in which it was tested. That is very clear. What is complicated is going from there -- and I am going to be dependent on Dr. Livengood about this contract that we have established because I don't know all the precedent there. But the lesion is translating that information back to the U.S. population. And the barrier that has been imposed is the recent identification of a relationship -- recognition of a relationship between pertactin and fimbriae and also pertussis toxin and antibodies against those molecules and protection. Although there is some order given to

that, there are no absolute and there is no threshold with which we can say this is or isn't. It is not like tetanus toxoid, which you can say if you have this amount, you are assured of being protected.

There also -- Bruce Meade summarized this very well -- it certainly is possible that these antibody levels are surrogates for something else. We can't tell that for sure at the present time. So I am really concerned that we -- I personally can't get away from looking at the other array of vaccines that are available on the market. I know we are supposed to do this based simply on these data, but I can't get away from thinking about it that way. I believe -- we talked about what if you take pertactin away from this or any of these vaccines. And I know that the SmithKline vaccine, the two-component vaccine is not identical to the Infanrix that is on the market. But they are very similar products and they are very different in efficacy with and without pertactin. So from all the cumulative data, personally I am a big believer in we are adding more and more antigens. The point that was made is we are reconstructing the whole cell vaccine in a manner of speaking, and now we are asymptotically approaching the point where the incremental additions are very small.

So I do think that pertactin is important. But I also believe that we don't have the data to say that if there is a marginally decreased pertactin response in the population that that is enough under these circumstances to judge this vaccine inadequate to be used in the U.S. population. And we could easily run around this circle for a long time.

DR. GRIFFIN: That is what we would like to avoid.

DR. HEWLETT: Yes. I think we could do that. My personal opinion is from the data that are available, this is an efficacious vaccine and that this particular observation that has been made from my perspective is not enough to suggest that it shouldn't be licensed.

DR. GRIFFIN: Okay. Other comments? Yes, Dr. Kohl?

DR. KOHL: Dr. Hewlett, or your expert colleagues, can you think of a biological reason why this vaccine should be less efficacious in children in this country versus children in Sweden? Now one possibility is racial differences, and that hasn't been addressed. The data that I know of from the NIH studies suggest that in the small number of black kids that it was tested on, they actually had higher

antibody levels. But can you think of another plausible biological explanation?

DR. HEWLETT: I cannot. In fact, the data that were present here about maternal antibodies and higher pre-immunization titers resulting in not as good a response, I wasn't -- I didn't understand exactly why they ended up being sort of dismissed. Because that looked relatively convincing to me as a possible explanation.

DR. KOHL: And would that -- do you think that might then affect the efficacy of the vaccine? We know that in measles, for instance, that is the case. High maternal antibody levels would decrease the efficacy of the measles vaccine. Do you see that as a problem with this vaccine?

DR. HEWLETT: I think it depends entirely on when the vaccine is given and when the person is challenged with pertussis. So I can't predict.

DR. GRIFFIN: Dr. Katz?

DR. KATZ: I hope these remarks won't be taken as facetious. But I think that if we are really going to talk about ethnic, genetic and racial disparities, you've got to talk about an Asian population, you've got to talk about a Hispanic population, you would have to talk about a Caribbean

American versus African American. It just seems to me that you are going to have to decide -- and this may be FDA's job -- how many different groups are you going to have to examine. Are the Mong people in Minneapolis different than the Koreans in Los Angeles? They are very significant large populations. And I don't know that this particular vaccine should be held to that sort of examination at this point. But it is the sort of thing that anthropologists and demographers and geneticists can do if you license these vaccines or when you license these vaccines.

DR. GRIFFIN: Other comments on the efficacy issue? Yes, Dr. Livengood.

DR. LIVENGOOD: Let me go back and try to clarify a bit about what I was talking about about our sort of informal agreement, if you will, to license things based on similar immunogenicity. If pertactin had come out the same as in the Swedish children, we wouldn't be sitting here having this meeting right now. So clearly there is enough of sort of our belief that our agreement was good to license based on that to at least convene this committee to look at that. I am not saying necessarily that that was the wisest decision. I mean, it was a decision -- it certainly is not the most scientifically valid, because even if the

antibody titers are the same, does that mean the protection is the same? We don't know. As we have heard, we don't know what about the vaccine protects. We never knew what about whole cell vaccine protected, or else we wouldn't be trying to rebuild the organism through different strategies now.

So I think that there is really fairly good evidence though that we could set aside that previous agreement and look at this. And that is one of the reasons we are here. I think the reason we are asked the question about the fourth dose in particular is because there are data that after the fourth dose the antibody profile in American children looks like that after three doses or better than the Swedish children. So therefore even by this sort of informal agreement, we would have to sort of follow into agreeing that the data support efficacy after four doses. I personally would rather us focus on the three dose because in my past I represented the National Immunization Program and I am not particularly interested in the concept of really needing a four dose series and potentially leaving children suboptimally protected between six months and 17 months of age with this vaccine, and then how would you do it in our pluralistic society where children

get multiple different vaccines and multiple different types of vaccines.

So I'd like to see us really try to focus in on the three dose and whether we think that the pertactin difference, which appears to be real, but does it mean anything. And if it doesn't mean anything, then try to deal with it in that manner. I am not necessarily saying I think that it is an important difference. It is a difference and I hope that we could in some ways try to deal with the three dose series instead of reconceptualizing this vaccine as a four dose basic series for program implementation.

DR. GRIFFIN: Dr. Midthun would like to help clarify the situation here.

DR. MIDTHUN: I just wanted to get some clarification with regard to what you meant with regard to the agreement.

DR. GRIFFIN: Well, I was going to ask the same thing. I think it would help all of us to know what -- because partly to know whether we are setting some precedent if we say we think this vaccine is -- despite the fact that it is not equivalent. Or what the historical context is in which we are working.

DR. LIVENGOOD: Well, I think there was a

lot of concern very early on that we would do these trials abroad and then the FDA would say, we need trials in the United States to know if this is effective in American children.

DR. MIDTHUN: Right. So I think what you are basically saying, and if this is what it is, I would agree. I mean, I think that there was an understanding that efficacy trials would be performed and that then because one wasn't able to do an efficacy study in this country that there would be a mechanism to bridge those efficacy data to the U.S. population and that those would be by way of obtaining good safety data and also by looking at the immunologic responses. I think that -- so if that is what you mean by agreement, I think certainly that was the way that we thought we would evaluate these data.

DR. LIVENGOOD: Yes. I don't mean to interpret -- to suggest by using some of the language that there is a formal written agreement or law. I am just saying that there was then an assumption that that is how the FDA would proceed. And I think that if there were no difference in this pertactin, we wouldn't be debating whether this was efficacious. We probably would have -- we would have come, but we would have been out of here by lunchtime probably

instead of obviously the large amount of work the staff and the sponsor put into doing lots of other analyses trying to allay any concerns we might have because of that. So that is what I think the major issue is. And it would help me come to a decision about this if I could hear what some of the other members felt about that. Because frankly, I don't think from the world of pertussis that there is a lot -- you know, there is no special expertise that somebody is going to stand up and put a graph up and, oh, that is it. It is not pertactin at all, it is a ratio. It could be anything and we don't know what it is. And we are just going to have to make a decision at some point as to whether this one difference in one component is in fact evidence of a potential or a real difference in efficacy between the Swedish population and the American population.

DR. GRIFFIN: Dr. Fleming?

DR. FLEMING: I'd like to go back maybe to the questions that I am troubled by that I would like to have whatever guidance and insights the committee could provide. That certainly would help me in answering this efficacy question. I think of three issues that we have talked about. One is when we say is there adequate efficacy, exactly what do we mean by

that? I can think of three examples of what might be meant, and there are probably numerous others. One is evidence to be able to conclude that you can rule out no efficacy. Well, if it is that simple, I think the answer is yes. I am comfortable that the answer is yes. We can rule out no efficacy. On the other hand, typically we have asked for more than that for vaccines. So maybe it is evidence to rule out efficacies less than 70 or 80 percent. Well, if that is the question, I think the answer is yes for the three dose vaccine in Sweden based on the quality Swedish Trial that has been done.

Another is asking for non-inferiority relative to a good whole cell vaccine. And there I would say the answer is not established. We have non-inferiority relative to a whole cell vaccine in Swedish I, but I am told that is not one that counts because that is not a particularly good whole cell vaccine. We don't, however, have adequate non-inferiority established even by what was a clear pre-specification of the standard that was set for the Swedish II Trial. And in particular, in addition to the fact that we didn't hit the pre-specified relative risk -- being able to rule out relative risk of 1.5, we also have what troubles me greatly, which is

significant under-reporting post-dose three.

So I would like to see if any of those three definitions are what we should be using or is there something else? So that is question one.

Question two is --

DR. GRIFFIN: Do you have a suggestion?

DR. FLEMING: Let's come back to that.

DR. GRIFFIN: All right.

DR. FLEMING: In fact, before giving a suggestion, I really would like to hear others. I have given three, one of which is easy to answer, but it is not one that would satisfy me, which is ruling out no efficacy.

The second issue is the Swedish versus -- the bridging issue, the Swedish versus the U.S. population and what is the bridge. What is the measure? Is it some type of antibody activity? Is it cell mediated immune response? Is it memory? Is it what antigens? What difference is meaningful? I would like to have a sense of what that answer is, the statistician in me coming out here, if I am going to then answer the question, yes, these data do or don't establish that level of effect on that specific bridging measure. What is the bridging measure and if at all possible what is the argument for this being

the best bridging measure?

The third issue is I hope maybe an easier one to answer, and that is if we are being asked for efficacy about four doses as well as about three, and we obviously don't have the data on four doses, can we all more or less assume that when you go from three to four, the question is are you enhancing safety in a way that is a concern? But when you go from three to four, if you have established efficacy for three, you are confident that the efficacy for four would be at least as large as three? If the answer to that is yes, that is at least going to make that third issue easier to address. So I actually would like to hear what others think about these three issues.

DR. GRIFFIN: Okay, why don't we start with issue number one, which is what kind of --

DR. FLEMING: What do we mean by efficacy? What is the standard that we would expect or that we would wish to be able to conclude exists when we say there is efficacy? Is it a non-inferiority comparison to a good whole cell? Or is it a comparison to a placebo that establishes a given level of protection?

DR. GRIFFIN: Would anyone like to offer an opinion from a general point of view on which of those -- which of those two really that we are trying

to establish here?

DR. HUANG: I will tell you what I have learned on this committee over the years, and that is that if you have an absolute efficacy, that you are looking for something like 70 percent or better. And certainly if you are in the 80 percent, you are pretty comfortable with that.

Let me address the second issue, which is these immune markers. I have to say that I walked in here being very worried about the use of the marker and I was very worried about the antigen that did not elicit a response in American children. And I wish that we didn't have that data to look at. Because if I just had the Swedish I to look at, I would say fine. This is a great study. We need it. We can use this here. But given the fact that we now have this extra information, it made me look back on what I knew about viral vaccines and most of the mechanisms of the viral vaccines are really unknown. They work. They really do protect. And in fact, we will be seeing coming down the road HIV vaccines that elicit a huge amount of antibody but don't protect and HIV vaccines that elicit no antibodies and are now beginning to see as if they are protective. So I think that as we go down this road more and more in looking at vaccines, we are

going to throw away those immune surrogates and use them only if they positively correlate. But if they negatively correlate, we are not going to use them.

DR. KATZ: I don't know. Diane and I may disagree with you.

DR. GRIFFIN: Right.

DR. KATZ: I think you can't lump microbes. I mean, if you take your example, if it is an enterovirus, antibody is everything. If it is measles virus, it is CD4 cells and cell mediated immunity. We use antibody as a surrogate because most laboratories aren't going to measure cell mediated immunity, other than research laboratories. You can't send a specimen off from your hospital lab or your public health lab and get cell mediated immunity done. So that antibody is a more pragmatic surrogate, but not necessarily pathogenetic. It is only reflective.

DR. GRIFFIN: But also not necessarily unrelated to the protective efficacy.

DR. KATZ: It absolutely can be related. But in the absence of antibody, as in the congenital A-gamma patients, the X linked A-gamma globulinemics, they can handle a measles infection, but they can't handle an enterovirus infection. I think it is just a good example. If we are talking about bacteria here,

not viruses. I would like -- maybe John Livengood can comment about this. We are talking about a moving target. When you compare Sweden and Germany versus the United States, you have already discussed why the studies were done there. They weren't using pertussis vaccine and they had disease. We don't have disease. But we do have disease, and if you look at the age groups in which disease occurs -- and here is where I need John to keep me honest -- it is the young infants under a year of age and it is adolescents and adults who are getting pertussis today. And I think the moving target is, one, we are looking at vaccines that might be effective in boosting adolescents and adults because we know none of the pertussis vaccines produce enduring or life-long immunity. It may be 7 to 10 years.

Secondly, you've already mentioned repeatedly that we are looking at vaccines that are licensed and widely used that have no pertactin at all. And we are holding this hostage to a different standard with no evidence that it is in any way a liability. It is only a hypothetical or theoretical one.

DR. STEPHENS: Can I clarify an issue that is -- we are talking largely about pertactin as an

immune response. But I thought the data suggested that those individuals who had a lower response to pertactin, the entire range of antigens was in fact decreased. Is that not correct?

DR. MEADE: Yes, I did put up one slide that suggested that the other -- there was a trend for lower responses to the other antigens in those individuals. Again, we did a stratification based on again an arbitrary cutoff. But the sponsor did the same thing for other cutoffs. So the answer is, yes, they generally did have a lower response.

DR. STEPHENS: And was that correlated at all with a maternal antibody -- that particular group of individuals?

DR. MEADE: I would have to defer to the sponsor to see if they did look at that. Again -- so the answer is I don't know that. I mean, I should -- since I have the microphone, I should comment on the one comment that Dr. Hewlett made. Again, in the one study that was presented in detail this morning by the sponsor, there was -- appeared to be a significant negative correlation between maternal antibody of pertactin and the subsequent response. But in the NIH multi-center trial, they did a similar analysis. And there there was no significant relationship. So we are

faced with one study where it correlated and one where there was no significant correlation. We really didn't -- it seems like a generalization that based on what we know now is not possible. So that was the observation. I think it certainly needs to be explored because it is probably multi-components that either AHN or maternal antibody or any other factors that we haven't investigated. And it should be looked at further.

DR. GRIFFIN: Dr. Kohl, did you have your hand up?

DR. KOHL: I did, but I am starting to get cold feet waiting, which is unlike me. I just leap in. Efficacy -- efficacy is disease prevention. And there is no question in my mind that this is an effective vaccine based on the Sweden I study in particular, but also I think corroborated by Sweden II. The third question you asked was the fourth dose, I believe. The efficacy, I think you asked, of the fourth dose. To my knowledge, there are no efficacy on fourth doses. All the efficacy data is in the primary series. So when we are talking about fourth dose, what we are really asking efficacy-wise is what is the increased time of protection that the fourth dose gives you. And there are no data in any pertussis

vaccine, except possibly whole cell, and I don't even know that for a fact, on that. So that is a question that we can't answer. And that has never been used to license the fourth dose. So I think that question is moot.

And then the most important or at least the hang-up question here is the bridge question. And I would agree with I think Sam in terms of not having this very effective vaccine held hostage to the response to one component, which is not included in two license vaccines, and which I am not sure what its role is in a multi-antigen vaccine. So I feel comfortable with the bridging data as it stands. Also, again corroborated by some of the data showing that after two doses, albeit with a different vaccine slightly, that after two doses the immune response was essentially equivalent to after three doses in the U.S. But I am not using that as my primary reasoning. I am using it more of my biological understanding of this vaccine. I'll stop.

DR. GRIFFIN: Okay. Other?

DR. MEADE: I think I need to, again, make a couple of clarifications. Again, I am trying to go through this. I may ask Dr. Midthun to fill in since she is familiar with some of the specific points on

some of the trials. But you commented that all of the trials used a -- were based on three dose series. The trial for the Acel-Immune product did include a four dose. And much of the data and the data in the labeling related to for the Acel-Immune is based on a four dose -- is based on the efficacy as demonstrated. There was estimates of the efficacy after three doses. But the primary -- as I recall, the primary outcome was after four doses. And then the other issue, and again it relates to one of the other license products relates to the -- and again, I am going to ask Dr. Midthun to fill in on the issue regarding the labeling of Certiva and the issues related to that product.

DR. MIDTHUN: I think for perhaps a little bit of clarification about the way the question has been stated, I don't think that we were asking about efficacy per se after four doses. Because you are right, we don't have any data on that. I think the question had to do more with if there was not quite the ability to bridge with regard to pertactin to a three dose schedule in U.S. infants, but there was actually a higher level of pertactin antibody achieved after the fourth dose was given to U.S. children, how would that be viewed in terms of trying to extrapolate data after three doses in Sweden to a four dose

schedule in U.S. infants. But to get to the issue that Bruce had raised or Dr. Meade had raised, we had a situation with Certiva, which was another acellular pertussis vaccine, which is just a monocomponent pertussis toxoid vaccine, and it was evaluated in a Swedish efficacy trial also, but it was administered only on a 3, 5 and 12 month schedule. So that the only efficacy data we had from that study was on that particular schedule. And that was obviously difficult because in this country the infants get vaccinated at 2, 4 , 6 and then usually a booster given to the toddlers. And what was done in that particular study was that there was actually a bridging study first done in Sweden where they either gave infants vaccine at 3, 5 and 12 months or at 2, 4, 6 and 15 months of age. And they looked to see what the antibody responses were after the third dose. And what they found was the antibody response was significantly lower after the third dose given on a 2, 4 and 6 month schedule as compared to after a third dose on a 3, 5 and 12 month schedule. However, if you looked at the responses after the fourth dose on a 2, 4, 6 and 15 month schedule, that was very similar to what you saw after a third dose on a 3, 5 and 12 month schedule.

There was a study then done in the U.S.

where again they also looked at the antibody responses and they found that really 15 months after the fourth dose, 15 months on the U.S. schedule, that you were very comparable to where you were after a fourth dose in Sweden on the 2, 4, 6 and 15 and also after the third dose at 3, 5 and 12, which is where the efficacy study lay. So it is sort of a complicated bridge that we had to resort to in that study because that is the only efficacy data we had was with that particular schedule. I don't know, maybe I have confused things more than I have helped things.

DR. GRIFFIN: Well, you have reassured us that it is complicated. Dr. Faggett?

DR. FAGGETT: I think it might be helpful to us as a committee -- it sounds like we have a -- I am comfortable with the three dose. We might have a consensus pretty much that that looks like an effective regimen. Let me just register one comment from Dr. Manley, who had to leave. She was very concerned that we do need clinical trials data from the U.S. before we can really make a decision. She would not be comfortable to support going forward without that data. She was very clear on that. So that is from her. But would it be possible --

DR. KOHL: Clinical efficacy trials?

DR. FAGGETT: Say again?

DR. KOHL: Clinical efficacy trials?

DR. FAGGETT: No, just clinical trials.

DR. KOHL: What kind of clinical trials is she talking about? Did she tell you what kind of trials?

DR. FAGGETT: She didn't say what -- she didn't specify. But her concern was that the Swedish data was not -- was not as impressive to her in applying it to the U.S. population. So she is really --

DR. GRIFFIN: I guess a problem for efficacy trials is that we are not going to be able to do those in the United States.

DR. FAGGETT: Right. But I think -- well, let me just -- that was just her reservation. She asked me to state that for her.

DR. GRIFFIN: Okay. Other comments or questions? Yes?

DR. KATZ: My question is for John Livengood again. Are they still using whole cell -- is whole cell still the vaccine in the United Kingdom? DTwP? And what is their schedule? They only use a three dose schedule, don't they?

DR. LIVENGOOD: They are currently

evaluating the possibility of instituting a fourth dose. But they only use a three dose primary series, yes. They are talking about a fourth dose in toddlers right now, but they haven't come to a real conclusion on that.

DR. GRIFFIN: And it is a whole cell vaccine? Is that right?

DR. LIVENGOOD: It is not a 2, 4 and 6. It is a 2, 3 and 4 month.

DR. GRIFFIN: Okay. Dr. Meade?

DR. MEADE: Whole cell was the predominant product used in the UK until fairly recently. But I understand that is very much in transition. And someone from the UK would have to respond to that. I don't think that is -- my understanding is whole cell vaccines are not currently available in the UK and they are making a transition to acellular. Someone who is more familiar with the situation should comment on that. But certainly up until recently, whole cell was the product used in the UK.

DR. GRIFFIN: Okay. Anything else? Do people feel ready to vote on this issue? Yes?

DR. MEADE: I am wondering if I should comment -- make sure again I reinforce Dr. Midthun's comment. Again, the wording of these questions is

extremely complicated and we always never quite hit it right. Because we are asking very complicated questions. But I think it is important to clarify --

DR. GRIFFIN: Would you like to restate your question in 1A?

DR. MEADE: I will try to explain the question that we know how to answer or that at least we think there are data to address. I mean, that is -- the question 1A really is are the data -- are there data -- for this product for which there is efficacy data, is there evidence that the efficacy was shown in Sweden. But we have asked the question for the U.S. And so the question is are the data that are available in the U.S. indicative that the data that we are seeing in Sweden would be applicable to the U.S. And I think we have asked it intentionally as a two-part question. First is did they meet the criterion after four doses? And then if that question is answered yes, then we need discussion on what conclusions can be draw after three doses. So I think it is important to clarify that the fourth dose question relates to have they, based on the efficacy data in Sweden combined with the bridging data in the U.S. and the immunogenicity data in the U.S. shown sufficient evidence that the efficacy in the U.S. after four

doses would be comparable to what was observed in the Swedish Trial.

DR. GRIFFIN: Okay. Dr. Goldberg, did you have another comment?

DR. GOLDBERG: I just had a question of clarification. I don't know if this was done or I missed it. When you presented the data on the maternal -- on the age of immunization and the maternal titers, was there any point where you looked at -- for a group that was exactly -- if you took the group that was in the U.S. bridging study that had ages comparable to the population in Sweden, what the results were? Because it is possible since these titers change with age at immunization that if we restricted the U.S. -- if we stratified the U.S. bridging data by age and looked at the exactly comparable group, it would be interesting to see what that looked like, and that might clarify some of this. I wonder if you have that data available or anyone has looked at that?

DR. GEBER: I think perhaps the sponsor can address that for the U.S. Bridging Study. I think other than what Dr. Meade mentioned previously, that it was borne out in one study but not the other. But in addition to that, as Dr. Meade mentioned, the Canadian studies where the lower pertactin level was

observed were almost universally given to children of an older age group comparable to I believe what was given in Sweden. We did not see analyses presented for those studies comparing maternal antibodies, and I think that the FDA's conclusion that we could not make too much of those data in terms of causality were based on those observations. Not that it doesn't play a role.

DR. GOLDBERG: I just think it might inform this discussion because the populations are so obviously different. But there is overlap. So it would be just an interesting way to cut the data to see if that could clarify any of this.

DR. GEBER: But apparently the Canadian children were immunized at a age that was similar to the Swedish children, right?

DR. GOLDBERG: No, I understand that. It is just that we are trying to build this bridge with the U.S. data. Can the sponsor address this?

DR. XIE: My name is Fang Xie from Aventis Pasteur. We have looked at the data stratifying by age. We stratified for both the U.S. Bridging Study and the Swedish Trial I with less than 50 and above 70. And when you looked at the stratification for the age greater than 70 days at the first immunization,

the U.S. Bridging Study virtually has the same antibody level as in Sweden. However, the U.S. Bridging Study has much fewer numbers.

DR. GOLDBERG: I understand.

DR. GRIFFIN: How about when you look at it the other way around? If you look at the youngest children in Sweden?

DR. XIE: Well, unfortunately, there aren't many younger children. Most of them are under -- sorry, above 60 days at the first immunization.

DR. GOLDBERG: Well, what if you just took it from 60 days and you went --

DR. GRIFFIN: Please use the microphone.

DR. GOLDBERG: What if you looked at it from 50 or 60 days in the U.S. on the above?

DR. GRIFFIN: That is what he just --

DR. GOLDBERG: You just gave me information about 70 days.

DR. XIE: Right. when you look at above 60 days for both populations, you see the -- for the U.S. population, you see the same phenomena as you see in Canada, which overrode the antibody responses lower.

DR. GOLDBERG: Thank you.

DR. GRIFFIN: Okay. Dr. Fleming?

DR. FLEMING: I have a question kind of

following up and maybe a question for Steve. But I guess in the process of asking my question, I will be giving my answer at least as I see it right now to this efficacy issue.

DR. GRIFFIN: Okay.

DR. FLEMING: I still see it as two potential standards that we might be asking to be achieved. One of those standards, and this is my sense of what you were saying -- one of my standards could be is there reasonably adequate evidence to establish that we have the efficacy that other marketed acellular pertussis vaccines have? And so if we go to the Swedish Trial I, where we see 85 percent efficacy against 58 percent efficacy for the two-component vaccine, and we say even though we have this pertactin question, is it still highly plausible that we are at least maintaining the 58 percent efficacy -- if that in essence is your argument, I think that is rational to argue that that is the case. On the other hand, if we are saying we are in essence looking at a whole cell pertussis vaccine, a good one, that is potentially though a vaccine with safety risks that we would like to be able to reduce, typically we would say but only allowing a certain amount of efficacy to be given up, and I will use the standard that Swedish

II set, 50 percent higher risk is all we would tolerate. If that is our standard, then I believe we haven't established adequately that we can rule out with reasonable confidence that there isn't one-and-a-half or more fold increase in transmission risk. I would argue that first of all because the Swedish Trial in its own right doesn't establish that even in Sweden, without even getting into the issue of uncertainties with the relationship of efficacy in the U.S. versus efficacy in Sweden. So I guess if I were answering the question, I am going to toss it back to the FDA as yes, if, but no, if. Yes, if it is enough to say this is highly plausibly as effective as other acellular vaccines that are out there already licensed. But, no, if we want to be able to say with adequate confidence that we are not meaningfully worse than a good whole cell vaccine.

DR. GRIFFIN: Okay. Any other comments? Do you have an opinion about which of those two questions we should be -- I think we are going to have to -- people are going to have to target their answers. Or they are going to have to explain when we go around, I guess, and vote, what the standard is that they are assuming or what their criterion is for -- maybe that is the easiest thing to do rather than

try to reach some consensus.

DR. KOHL: Could I remind Tom -- that whole cell vaccine is a European whole cell vaccine. That is not licensed in this country. So if you want that whole cell vaccine, you are going to have to get that licensed in this country. Right now we have acellular vaccines that are licensed.

DR. FLEMING: Which makes it even harder to answer the second question yes to my way of thinking.

DR. GRIFFIN: Okay. Are people ready to vote? Okay. I am going to start at the other end of the table. Dr. Hewlett?

DR. MEADE: Can you -- I think it is important to be sure that the question -- again, make sure that the question we are asking for a vote on is whether or not -- is the question 1A. Would it be helpful if I read that to be sure? Again, I think there is -- and that is, are the data adequate to support the efficacy of the acellular pertussis component of CPDT when administered to infants and children in the U.S. as a four dose series? And if not, what additional information should be requested. So I think we are asking specifically the first question is whether or not after four doses in the

U.S. that they have met the criterion. And basically we are asking for comparability for the bridging criterion to Sweden for when this vaccine was actually evaluated directly in an efficacy study.

DR. KOHL: And Bruce, after four doses the pertactin antibody levels were high.

DR. GRIFFIN: Right.

DR. MEADE: Correct. They were -- we broke them out and they were in all cases --

DR. GRIFFIN: I think that -- I mean, I guess part of the -- as you say, it is always hard to structure these questions. But this becomes a two -- this question has two components to it in a way. Because we are not all saying that the antibody data itself is equivalent to efficacy. But in a way, that is what you are asking in this question, I think. Right?

DR. KOHL: But I don't know what the question means. Because if we answer 1A yes --

DR. GRIFFIN: That is what I mean. It is two things. Efficacy is one thing and antibody response as being the same is --

DR. KOHL: What I mean is if you answer 1A yes but 1B no, where does that leave you?

DR. MIDTHUN: I think that maybe one way

to look at the question -- and I think you are right, Dr. Griffin. I guess one question is was efficacy demonstrated in Sweden 1. That is one question. And then the second part of that question is do you feel that these efficacy data from Sweden I can be extrapolated to the United States based on the data you have seen. And the first part of that question is assuming that you would be vaccinating these infants and 2, 4, 6 and 16 to 20 months of age or whatever. So I think maybe if we can think about breaking it down like that, whether that might be helpful. No?

DR. GRIFFIN: How about if we answer the very first question that you just said. Was efficacy demonstrated in the -- for this vaccine in the Swedish Trial? Then the second part of that question is are the bridging data adequate if we are dealing with four doses? Because that is what I take your second half of that to mean. Okay?

DR. MIDTHUN: Yes, that is correct.

DR. GRIFFIN: All right.

MS. CHERRY: Let's give them a moment to formulate their answers and then ask the second part of the question.

DR. GRIFFIN: Oh, sure. Excuse me. We have a procedural thing. You are almost ready. We have --

on the agenda are two open public hearings. So I need to ask if there is anybody else who would like to address the committee in open public hearing before we vote. Seeing no one, we may proceed.

DR. HEWLETT: Now I forgot my answer.

DR. GRIFFIN: Worse, you have probably forgotten the questions.

DR. HEWLETT: I think the way that it was just -- the way that Karen just put it simplified things. I believe that data from the Sweden I Trial is adequate to show efficacy. And if we talk about the fourth dose, which as Dr. Kohl pointed out results in high titer anti-pertactin antibodies that are comparable to or I believe higher even than what was demonstrated after three doses in Sweden, then that makes -- for four doses, that makes that problem go away and I think that is adequate.

DR. GRIFFIN: Thank you. Dr. Livengood?

DR. LIVENGOOD: Yes. I would agree with that. I believe the Swedish Trial, which the FDA also concurs, demonstrated high efficacy of this vaccine sufficient to warrant its licensure in the United States. The bridging data through to the four doses are also adequate to show that we can produce antibody titers in children in America. But that is all the

bridging study can do. But that is what we asked it to do and I would agree with this.

DR. GRIFFIN: Thank you. Dr. Myers?

DR. MYERS: I agree with them.

DR. GRIFFIN: Dr. Fleming?

DR. FLEMING: I certainly commend the sponsor for having done an outstanding study with Sweden Trial I that I think clearly establishes efficacy in Sweden. And as I had mentioned before, I believe if we are essentially only meeting to conclude that efficacy in the U.S. would be at least comparable to that of a marketed acellular pertussis vaccine in this country, I think it is adequately plausible to conclude yes as well. If, on the other hand we are looking for adequate evidence to establish non-inferiority to a wholesale pertussis vaccine, I don't believe the evidence for that is adequately strong. And I am jumping ahead, but because I have difficulty in even interpreting the serology data, I think the answers that I give will be the same for the three or four dose.

DR. GRIFFIN: Okay. Thank you. Dr. Goldberg?

DR. GOLDBERG: I think that the Swedish Trial does establish efficacy for an acellular

pertussis vaccine. And the serology data also still troubles me. So I really don't know what to say. I am going to hold off.

DR. GRIFFIN: Okay. Dr. Faggett?

DR. FAGGETT: I must have been having a senior moment there, Steve. Thanks for trying to get me back. I think first Dr. Manley really said that we needed more efficacy studies for the U.S. She did not accept the Swedish studies as being applicable. So she would vote no for the first question. We do not have enough data based on that opinion.

I personally -- it sounds like we do have a new standard with pertactin now. Are we indeed really now saying that that is a requirement to be an effective vaccine? So it is a whole new ballgame. But it does sound to me -- my opinion now -- that we do have some demonstrated efficacy from the Swedish study. I think the fact that we don't have data in terms of the fourth dose, I have real questions. But I have to defer. I will defer in this case to some of my more knowledgeable colleagues and go along that this should be an effective vaccine for the U.S. population.

DR. GRIFFIN: Okay. Ms. Fisher?

MS. FISHER: If you don't understand

qualitatively and quantitatively which components of the vaccine or individual host factors are responsible for immunity, just like if you don't understand which components and host factors are responsible for reactions, I don't think you really understand what you are doing. For example, if you begin to see pertussis in a highly vaccinated population, which is being seen in some European populations, it is going to be very difficult to understand why and how you need to change the vaccine to make it more effective. And I think at some point we are going to have to stop grandfathering in vaccines using old standards that are more based on assumptions and lack of understanding than on scientific knowledge. So I really feel like with the first question with safety that we have to hold a trial in this country and start to answer the outstanding questions.

DR. GRIFFIN: Dr. Diaz?

DR. DIAZ: I would agree with the first aspect, which is that the Sweden I study does demonstrate efficacy in Swedish children. Without a doubt in my mind based upon the parameters that were set at the times that the children were looked at and also in terms of outcome. The bridging study I would also agree with one of my other colleagues that made

the comment that it definitely shows that this vaccine can develop and produce antibodies in children in the United States. I am a little uncomfortable in that I don't quite -- obviously, we don't have all the answers or again we wouldn't be sitting here today. And how much the reduced pertactin antibody response in the United States children really plays into efficacy, we don't know.

DR. GRIFFIN: Are you talking now after four doses or three doses?

DR. DIAZ: I am talking after three even. I would probably again say I realize that after four doses, the antibody response to pertactin was greater than in the United States, at least it was adequate most definitely. So that wasn't as much of an issue. And yet again as Dr. Kohl pointed out, efficacy is disease prevention. And a large number of our cases of pertussis occur in children under the age of six months, who perhaps have the opportunity to receive one or two doses of a vaccine. So I don't know, and I don't have an answer. And yet, I am not sure how to interpret the bridging data because of those issues.

DR. GRIFFIN: Dr. Kohl?

DR. KOHL: As Jack Nicholson said, this is a good as it gets. So in the year 2000, I would vote

yes, yes.

DR. GRIFFIN: Dr. Huang?

DR. HUANG: I certainly believe that the answer to the first question of the Swedish studies is that it is -- it has shown efficacy. For the second one, I am impressed by the uniform increase in immune response to pertactin after the fourth dose. And using that as the only criteria that we really have right now and as a positive correlation, I also vote yes on that.

And finally, I would like to make just one comment about diversity issues. As a member of a minority on one side of the Pacific and a majority on the other side of the Pacific, let me just say that I think that scientifically when we look at our own genetics that we are all somewhat mongrelized and that our immune response and our host defenses are much more in line with our HLA type rather than to our skin color.

DR. GRIFFIN: Dr. Katz?

DR. KATZ: I vote yes, yes on both issues. My caveat would be that Dr. Livengood get busy reevaluating the entire U.S. immunization schedule for the first two years. We are giving too many vaccines. Maybe he can teach us how to give fewer doses.

DR. GRIFFIN: Dr. Estes?

DR. ESTES: I vote, yes, that efficacy was demonstrated in the Sweden I Trial. I have reservations and actually vote, no, I am not convinced that this can, based on the bridging data, is adequate to come into the United States for a four dose immunization. I really would have liked to have seen data from four dose -- more data from four doses.

DR. GRIFFIN: Dr. Stephens?

DR. STEPHENS: There is also a danger in being last.

DR. GRIFFIN: Well, you can't have it -- give me your preference.

DR. STEPHENS: Very quickly, I think the data from Sweden is solid and that answer is clearly yes. I think the issue of the fourth dose is a little bit of a quandary since we don't have -- given the safety issues that we have discussed earlier. But I think that from the standpoint of immunogenicity that I would prefer to see -- I think a four dose regimen is -- so the second part is yes as well.

DR. GRIFFIN: Okay. And for the record, I would also vote yes, yes. Now we need to address -- many of you have addressed this as you went around. But now I think maybe just specifically to look at

question 1A, which is not really for a vote. I don't know, do we need more discussion of this? I think everybody can go around and say what they think about the third dose. This is not really for a vote. But we will give --

DR. MEADE: I think we would like to have -- again, for anyone who hasn't commented, to comment on the --

DR. GRIFFIN: The three dose issues.

DR. MEADE: The three dose issue, yes.

DR. GRIFFIN: Yes. Okay. So we will start again with -- I don't know, do you want to start? Let's start with Dr. Stephens first.

DR. STEPHENS: Sure. I am troubled by the three dose issue. I think certainly the Swedish data is very persuasive. Both the Swedish I study and the Swedish II study, even though the Swedish II study is using a slightly different version. But the -- I am a bit -- well, I am bothered by the immunogenicity data of the three dose regimen in this country. And I think that I have -- I would vote no for that particular aspect.

DR. GRIFFIN: Dr. Estes? Probably your --

DR. STEPHENS: Let me just comment. I think this is -- this is an excellent vaccine. It is

probably potentially better than some we already have out there. But I think the immunogenicity data is bothersome and I would like to understand that better before voting yes.

DR. ESTES: I don't have anything to add.

DR. GRIFFIN: Okay. Dr. Katz?

DR. KATZ: I am comfortable with the vaccine on a three dose schedule, and I think that many of the things we don't know relate to obviously the immunologic maturation that is going on in those first six months of life and what happens when a youngster who has whatever the titer may be is challenged. Do you have infection or do you have infection and illness? Do you have memory recall or so called reinforcement or booster dosage? I think there are a lot of questions to be studied and answered. But given what we know today, I am very comfortable with it as a three dose schedule.

DR. GRIFFIN: Dr. Huang?

DR. HUANG: I walked in thinking that I would vote no on this issue. But I have heard enough discussion and they are pro and con and I feel now comfortable with the three dose.

DR. KOHL: I want to take an old person's prerogative to welcome Dr. Katz to this committee. It

is just wonderful to have an absolute giant in the field of immunization on the committee. I wanted to make him blush too. I am honored to vote in the same vein as Dr. Katz did, yes. I feel quite comfortable with this as a very effective vaccine, and I see no biological reason why it won't be as effective in this country.

DR. GRIFFIN: Dr. Diaz?

DR. DIAZ: I don't really have anything to add. As far as the three dose, I would just abstain from the standpoint that -- the comments I made before about being somewhat uncomfortable. I don't have the historical perspective to perhaps put things in context to sway myself one way or the other.

DR. GRIFFIN: Okay. Dr. Fisher or Ms. Fisher?

MS. FISHER: I will let my comments stand.

DR. GRIFFIN: Okay. Dr. Faggett?

DR. FAGGETT: I will abstain.

DR. GRIFFIN: Dr. Goldberg?

DR. GOLDBERG: I will abstain in line with the comments I made before.

DR. GRIFFIN: Dr. Fleming? Three doses?

DR. FLEMING: Yes. I think similar to what I have been saying. If we take what I would consider

a fairly lenient stance of definition of efficacy, which is let's say is it at least comparable to the efficacy of the two component, I am persuaded by some arguments of colleagues that, yes, if I take the standard that I think I might have come in here with and still very much would find to be very defensible, which is non-inferiority relative to a good whole cell, I would say no.

DR. GRIFFIN: Dr. Myers?

DR. MYERS: I am very comfortable with it.

DR. GRIFFIN: Dr. Livengood?

DR. LIVENGOOD: I am troubled by the difference in the immunogenicity data, but I don't know what to make of it. I am not particularly worried one way or the other whether it is age of immunization or maternal antibody status. Because we will immunize our population the way we find them and whatever the cause of this is, we will likely see this as a real true finding in the population. I don't take any real comfort in the two dose data from Sweden II with a different vaccine, which I don't find very applicable. So I am stuck with a finding that I can't understand. And the way I read this question, are the data adequate to support efficacy, I would have to say no for three doses. I don't doubt that it is

efficacious, but I don't believe the data are adequate to demonstrate it.

DR. GRIFFIN: Dr. Hewlett?

DR. HEWLETT: I am afraid I am sort of in the same boat. I am a proponent of this approach and I believe that we are in a bind here, simply by virtue of the circumstances that we are in. I believe that this is a -- I know it is an efficacious vaccine under the circumstances which it has been tested. But from the information that we have here, can I prove that it will in fact work exactly the same way in our population? I don't think that we have that information. It is frustrating because I believe if I just had to go with my gut reaction, I think that it is probably fine. But the question says are the data that we are looking at adequate to support that, and there are some gaps there. And that bothers me because it is counter to my intuition.

DR. GRIFFIN: Well, I would actually agree. I am bothered by the differences in the antibody and I am concerned that pertactin might be important and having an immune response to pertactin might be important. And I guess what I would like to ask is if there is a mechanism for trying to figure this out. Either whether if it is a post-marketing

kind of thing, if there is surveillance or case finding for cases with pertussis and documenting what kind of vaccines they had gotten or whatever one might be able to do from an epidemiologic perspective to determine the importance of this component, I would like to see done. Do you have a comment?

DR. DIAZ: I was going to save it for the comment section, but I was going to bring up some of those issues. Maybe we can wait, unless you want me to make them now.

DR. GRIFFIN: All right. Okay, anything else on -- does this help you? Okay. All right.

DR. KOHL: Could you summarize how the committee voted? I couldn't keep track of that. Was there a vote?

DR. GRIFFIN: I think it was probably about 50/50. Nancy can give us --

MS. CHERRY: Yes, I think it was. If you give me a moment, I will do a -- I would rather do a whole count.

DR. KOHL: I am just interested.

DR. MEADE: As I said, we had requested a formal vote on 1A.

DR. GRIFFIN: But not on 1B. So it really doesn't -- it doesn't count. But they want feedback

basically.

DR. KOHL: Strike that question.

DR. GRIFFIN: Right. Okay. Now they also want comment -- and this is again not for a vote. On question 3, please discuss the adequacy of the data to support the concurrent use of CPDT with other vaccines administered according to the recommended schedule of infant and childhood immunizations. Please discuss additional information, if any, that should be requested. So, yes, Dr. Estes?

DR. ESTES: Well, I think -- in my opinion, the data certainly is not adequate, in particular with the changes in the polio immunization. There are no data. And so I think that is certainly something that is important to get some data.

DR. KATZ: Unless I misunderstood, I thought that what Dr. Mills presented to us was with inactivated polio. Is that correct? IPV?

UNIDENTIFIED SPEAKER: (Off the microphone.)

DR. GRIFFIN: That is a combination vaccine, right.

DR. KATZ: With their combination vaccine, which was DTaP, hemophilus influenza B conjugate, and inactivated polio. Am I interpreting -- so that was a

combination that looked highly successful. Okay. So I am comfortable. I think more needs to be done obviously and I think we need to increase our data base in the United States and there are studies underway with various groups. But I was comfortable with the Canadian data.

DR. GEBER: Just for point of clarification, those data have not been reviewed and are not really officially on the table. So perhaps we could limit our comments to the data -- concurrent immunization and the vaccine under consideration today, which is the classic formulation CPDT.

DR. GRIFFIN: Dr. Livengood?

DR. LIVENGOOD: I was trying to write down -- the numbers were extremely small. Like in the fourth dose it was 29 Hib and --

DR. GEBER: 135 in the fourth dose received concurrent immunization with hemophilus B conjugate vaccine and 505 received it concurrently with OPV. In Sweden Trial I, there were data on safety for concurrent immunization with IPV with the second and third doses on two-thirds, and there were data for concurrent immunization with hemophilus B conjugate in second and third doses on a third, but no immunogenicity data. All of the immunogenicity data

come from the infant series from the U.S. bridging study, and there were -- it was presented by vaccine lot. So I believe there were approximately 120 or 130 per lot -- lot 006 and lot 009 of CPDT from whom immunogenicity data were available with Hib conjugate. For OPV, their numbers were somewhat smaller, I believe an 80 to 70 per lot, so for a total of 150. And for hepatitis B, we were talking total if you combined the two lots of 80. There were no immunogenicity data with IPV, varicella and MMR or Prevnar.

DR. GRIFFIN: Dr. Meade?

DR. MEADE: I am sorry, I think I need to go back and make sure we have addressed the safety questions or issues on the fourth dose. I mean that was --

DR. GEBER: we were just discussing that we did want to get back to the issue of safety with the four doses. But we were having a discussion about whether just to continue along with the immunogenicity and then perhaps revisit the other.

DR. GRIFFIN: Come back and reformulate the question. Okay.

DR. MEADE: That is fine. I just wanted to make sure that we didn't --

DR. GRIFFIN: Forget this.

DR. MEADE: Forget to comment more specifically. We requested on the fourth dose whether the safety data would be needed pre-licensure or post. It could be evaluated post-licensure, which I think is an important issue to come back to.

DR. GRIFFIN: Okay. Any other comments first on the immunogenicity in combination with other vaccines? It sounds like --

DR. DIAZ: Are we voting on this?

DR. GRIFFIN: No.

DR. DIAZ: Oh, we are not.

DR. GRIFFIN: No. So it is just general comments and feedback. Yes?

DR. DIAZ: I recognize that there weren't a lot of fourth doses given, and yet I was a little bit disappointed not to see any data in combination with MMR in particular, and likewise potentially with varicella, although the precedent has not been to look at other acellular vaccines with varicella to this point. But nonetheless, I would want to see some data on the fourth dose in combination with MMR since a large number of our children, despite the fact that getting an MMR is recommended at 12 months of age tend to in essence get it at the same time they get their

fourth dose of DTP.

DR. GRIFFIN: Yes, Dr. Myers?

DR. MYERS: Because this is such a big issue, particularly as we get to subsequent vaccines, combination vaccines and so on, I have to say I think there is really insufficient data on the concomitant use of other vaccines -- varicella and MMR.

DR. GRIFFIN: Okay. That seems to be the consensus.

DR. GEBER: I am wondering -- we didn't ask for a vote, but I am wondering whether the committee members would comment on whether they feel that these data should be obtained prior to licensure or in post-marketing studies.

DR. GRIFFIN: Okay. Dr. Estes?

DR. GEBER: Perhaps that could be answered along with the fourth dose issue.

DR. ESTES: My own opinion is that they should be obtained prior to licensure.

DR. KATZ: I guess I would like to hear from the FDA folks how much data were required of the other acellulars as they were licensed in regard to combinations? Is this quite disparate or were there similarly small data which were enlarged post-licensure?

DR. GEBER: I think that the number of doses -- the number of doses of concurrent immunizations that were given were small. I think that our thinking has changed over the years and I think one of the difficulties we find ourselves in is this was an application developed early in the 1990's and submitted in 1996 and coming up for licensure today. So I would say that for the other acellular vaccines licensed several years ago, the numbers were smaller -- were small.

DR. KATZ: It seems to me there are two issues. Of course, one is the safety issue and reaction. If you have a "unfavorable reaction", to what do you attribute it when you are giving multiple vaccines. And that is going to be an issue that is going to haunt us increasingly as we do better with combination vaccines. That is not a simple one. That is not going to be answered with a couple of hundred or a couple of thousand. That is going to be post-licensure with tens of thousands. The other issue is immunogenicity. Is there any interference so that with one or another you diminish the immunogenicity of one or another product. And given the success of the currently licensed acellular vaccines, I don't see anything that we have heard that would lead me to be

concerned that this product would be more likely to interfere than the others. So I would vote for post-licensure surveillance.

DR. GRIFFIN: Dr. Huang, would you like to comment on these post-licensure/pre-licensure issues with respect to I think we are talking about really both safety and immunogenicity issues as far as its use in combination with other vaccines, which kids are increasingly getting more of.

DR. HUANG: We only saw data with diphtheria and OPV. Any others? I think with those I am pretty comfortable that the indications are that there are no problems in combining them. However, we haven't heard a thing about the others. And I think that I would prefer to hear something about it, no matter how small the population, before it is combined with many of the other vaccines that others have mentioned.

DR. GRIFFIN: Dr. Diaz?

DR. DIAZ: I think for the immunogenicity, I would want to see some data prior to licensure regarding MMR and other vaccines that we typically use in this country. This safety, I think -- I don't have any real reason to feel that that needs to be pre-licensure.

DR. GRIFFIN: So post-licensure monitoring. Ms. Fisher?

MS. FISHER: Oh, I think absolutely you have to have pre-licensure data. I mean as more vaccines and new vaccines are coming up, the public expects to have more data about safety and efficacy. And I think, again, my earlier comment, at some point we are going to have to move beyond the old standards into new standards. And I think they are going to have to be higher standards. So I would say pre-licensure definitely.

DR. GRIFFIN: For?

MS. FISHER: For the simultaneous administration of this vaccine with other vaccines. There is just such little data really that they presented. And in some cases no data. Children in this country sometimes get all the vaccines on one day -- 10 and 11 vaccines in one day. We have to have this information.

DR. GRIFFIN: Dr. Faggett?

DR. FAGGETT: Yes, I think we do have to have pre-licensure data obtained both from an immunogenicity as well as safety standpoint. I think the fact that pertactin is a whole new element in this whole ballgame, we need to see just how that plays

out. So I would say, yes, pre-licensure.

DR. GRIFFIN: Okay.

DR. GOLDBERG: The immunogenicity data should be pre-licensure. The safety can be post-monitored.

DR. GRIFFIN: Okay. Dr. Fleming?

DR. FLEMING: I am in agreement. I definitely think the immunogenicity data for combinations should be enriched and it should be done pre-marketing. The other question that we are going to be asked to address, which is the issue of enhanced understanding of safety, as I see it a big part of what we need there is the large scale experience that will allow us to address rare but important events. And I see that coming predominantly in post-marketing.

DR. MYERS: I think the immunogenicity data needs to be pre-licensure, particularly for IPV, varicella and MMR -- but particularly the IPV. As to the safety data, I think the amount of safety data available for the fourth dose is really marginal and so I think that needs to be pre-licensure. I think the other safety issues that we talked about could all be post-licensure.

DR. GRIFFIN: Okay. Dr. Livengood?

DR. LIVENGOOD: I would go along with

that. I would just add the pneumococcal vaccine.

DR. GRIFFIN: Okay.

DR. MYERS: I would add it to mine too.

DR. GRIFFIN: All right.

DR. FLEMING: I agree.

DR. GRIFFIN: Okay. Does that give you the feedback that you are looking for? Okay, question number 4 is please identify any issues that should be addressed by post-marketing studies. So other things that should be taken into consideration when this vaccine is licensed other than the things we have already discussed. I think the one thing that we hadn't -- that I just commented on and I think Dr. Diaz was whether we could build into any post-marketing studies some enhanced ability to understand what is protective and the role of pertactin antibodies or immunity in protection. Someone could study that. Other things that people would like to make sure are on the table for post-marketing studies? Okay. Well, thank you all very much for an interesting -- oh, excuse me. Just a moment. We have one more comment here.

DR. DIAZ: I thought we were going to comment upon those issues.

DR. GRIFFIN: Oh, yes.

DR. DIAZ: If I could for just a second. I think it is very important that we work towards strengthening our post surveillance, not just for perhaps this vaccine, but for all of the pertussis vaccines. There is still a significant amount of disease that does occur. And some of that disease occurs, obviously, in vaccinated children, albeit one, two, three or four doses. And although attempts are made, I think stronger attempts need to be made to really with disease to very much identify the type of vaccine that is given. And it is very difficult actually in case investigations to work back and sometimes even identify which, if there is only one, and sometimes multiple types of DTaP that have been given to an individual child. Additionally, I think that just bears in mind the need for stronger areas like registries and the ability to monitor things in that setting perhaps would be enhanced.

There are other issues I think that are coming to light. We have talked a lot about the antibody responses in the individual. There are also issues with the organism itself and the polymorphism of pertactin and pertussis toxin that has been investigated and recently reported. And how that will play into this country in terms of vaccine efficacy in

the long run is another issue that I think we need to start addressing in some of the surveillance systems that are already being developed in addition to saving isolates and looking at them very carefully when there is vaccine failure or disease period in addition to trying to get antibody and serologic studies on those children who fail vaccine.

DR. GRIFFIN: Okay. Other comments? Yes.

DR. HEWLETT: That is a very good point. I agree there is a lot of -- skepticism is not the right word. It is not clear exactly why the disease is occurring in Europe. Some people have put forth the hypothesis that it is the heterogeneity of some of these antigens. There is some skepticism about that. But absolutely we need to find out. And that is an appropriate thing to be doing in this context of post-marketing or whatever level of surveillance along with the safety and immunogenicity data to be looking at those kinds of issues. Do people make antibodies that correspond to an organism but that doesn't correspond to the vaccine?

DR. GRIFFIN: Okay. Dr. Midthun?

DR. MIDTHUN: I just wanted a clarification for the record. But if others were still going to comment, I will wait until the end.

DR. GRIFFIN: Okay. Any other comments? Dr. Huang?

DR. HUANG: We do know that the Swedish population is relatively homogeneous. I think it would be useful in trying to follow up as to the differences in immune response. If it is related to any of the factors that we know about, and one of them I mentioned before, HLA. I think that is -- if we can understand that, that would be quite helpful.

DR. GRIFFIN: Any other comments before Dr. Midthun seeks clarification?

DR. MIDTHUN: I know that on the last go around a lot of people specifically stated both for immunogenicity and for fourth dose safety data whether it would be required pre or post-licensure. But I am not sure that I heard that regarding the fourth dose safety data from everyone.

DR. GRIFFIN: Okay. Are we missing --

DR. GEBER: I think we were going to come back and address whether the size of the fourth dose data base was adequate to support safety. And perhaps some of us are unclear whether that specific -- in the absence of concurrent immunization.

DR. MIDTHUN: Just in and of itself, is the size of the fourth dose data base adequate? Is

the safety for fourth dose adequate? The safety data base for fourth dose. As I say, some people specifically addressed that.

DR. GRIFFIN: Okay. We will have everybody address that question specifically. Dr. Estes?

DR. ESTES: My answer was no.

DR. GRIFFIN: That is what I thought. Dr. Huang?

DR. HUANG: My answer was yes.

DR. GRIFFIN: Dr. Diaz?

DR. DIAZ: Yes.

DR. GRIFFIN: Ms. Fisher?

MS. FISHER: No.

DR. FAGGETT: Dr. Faggett votes no.

DR. GOLDBERG: Yes.

DR. FLEMING: I am on the fence, but I believe I am inclined to think it is all right, although I recognize that it is really limited for those that receive it before 17 months.

DR. MYERS: No.

DR. LIVENGOOD: I would prefer to see more data pre-licensure.

DR. HEWLETT: I thought that this was perhaps going to be made moot by the requirements for other immunogenicity data. I think the data are

limited. I think they are probably okay, especially since they are not inconsistent with other vaccines. But it will be important at one level or another to have additional data. I think post-licensure is satisfactory.

DR. GRIFFIN: Okay. So I think you have a split vote.

DR. MIDTHUN: Yes, we do.

DR. GRIFFIN: And for those of you who are interested, there was asked for a tally on the three dose regimens. It was four people no, five people yes and five people abstained. So we are sorry we are so equivocal, but I think maybe that is what the data are leading to. Okay. Any other issues that you would like further clarification of? Okay. Then thank you very much for everybody for participating. We will see you whenever.

(Whereupon, at 4:05 p.m., the meeting was concluded.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Vaccines and Related Biological Products Advisory Committee

Before: DHHS/FDA/PHS/CBER

Date: November 3, 2000

Place: Bethesda, MD

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.