may be due to the relatively small sample size.

This slide presents the incidence of fever following each dose and after any dose. As was seen in study 011, the incidence of fever greater than 38 degrees was increased in the group receiving the combination, compared with the separately administered control arm, although this difference did not reach statistical significance.

Again, this finding of non-significance may be due to the small sample size.

The incidence of fever was further evaluated in terms of the degree of fever greater than 38.6 degrees, or greater than 39.5 degrees. The observed incidence of fever greater than 38.6 degrees was increased in the combination, compared to the control, although this did not reach statistical significance.

DR. FLEMING: A clarification. You keep saying did not reach statistical significance. Can you go back to that previous slide?

DR. BALL: Okay.

DR. FLEMING: Confidence interval zero to 24.

DR. BALL: I'm sorry, as I pointed out earlier today, this was really right there in terms of

showing a statistical significance, right on the borderline, I mentioned that earlier, sorry.

This slide compares the incidence of fever in study 011 to that of study 015. Recall that the vaccination schedule study 011 was on a 3, 4, 5 month schedule, and study 015 it was 2, 4, 6 month schedule.

The incidence of fever greater than or equal to 38 degrees was fairly similar between the two groups, especially in the groups -- in the incidence of fever greater than 38 degrees centigrade.

The sample sizes for the two safety studies comparing the combination, and the separately administered vaccines were not powered to look at rare events.

I want to emphasize that, specifically events that occurred in the rate of one in several thousand. However, the rates of these events were looked at to see if there were any unexpected findings.

For this purpose the groups receiving the combination vaccine, and the groups receiving the separately administered vaccines, here labeled control, were pooled between studies 011 and 015, and the difference in the incidence was calculated.

Note that the sample sizes of the pooled

combination was much higher than that of the control, and thus the absolute number may appear larger in the combination group.

We are here focusing more on the incidence. As was mentioned earlier today, there were no cases of anaphylaxis, hypotonic hyporesponsive episodes, in addition there was no cases observed in the combination recipients for invasive bacterial disease.

Rates of hospitalization, death, and withdrawals due to adverse events were not different, were not significantly different among the groups receiving the combination, as compared to the control.

And, again, recognizing the limitations of this type of comparison, given the sample size, we looked at the incidence of seizures in the groups. For seizures over the full vaccination course, namely during the primary series, 2, 4, 6 months, and one month, to one month following the third dose, the absolute number of events appears higher in the combination vaccines, but there was no difference in the incidence of the seizures when the subjects receiving the combination were compared with the control.

In addition there was no difference

observed in the incidence of febrile seizures.

To further evaluate whether the increased rate of fever observed in recipients of the combination translated into increased hospitalizations, or increased evaluations for sepsis, or increased febrile seizures, we looked at the incidence of these events within seven days of vaccination.

The rate of hospitalizations, hospitalizations for fever and febrile seizures observed in the pooled groups receiving the combination compared with the separately administered vaccines was not different. Although, again, I stress the small sample sizes.

Now we will discuss data submitted to the license that addresses the safety of the primary series of the combination following a birth dose of hepatitis B.

With regard to studies filed with the license application there were no comparative trials examining the use of the combination with and without a birth dose of hepatitis B.

The application included the supportive study DTPa-HepB-IPV 030 in which all infants received a birth dose of the hepatitis B. Assessment of safety

data from this study was further hampered by the inclusion of the combination vaccine that contained wholesale pertussis as comparator to the combination vaccine.

The manufacturer submitted data from a related Infanrix based combination from study DTPa-HepB-IPV Hib, study 003, to provide supportive data. This study compared the primary series of this combination at 2, 4, and 6 months of age following a birth dose of hepatitis B with the primary series of this combination given without a birth dose.

In this study the rate of grade 3 fever, greater than 39 was somewhat higher in the group receiving a birth dose. The rate of local reactions appeared higher in the group that did not receive the birth dose.

Not shown here were data that were presented previously by the manufacturer on the incidence of any fever greater than 38 degrees centigrade.

Of note the rate of any fever for any dose defined as greater than 38 degrees was similar in the groups with and without a birth dose of hepatitis B.

Now I will present available data on concurrent administrations given in the primary

series.

Several studies in the license application evaluated the concomitant administration of Hib vaccine with the DTPa-HepB-IPV combination. Study 015 in the U.S. looked at one type of Hib, and supportive study 012 evaluated the immune response from four different Hib vaccines.

Study 011 different Hib vaccines were used but only safety was assessed.

This slide presents the observed immune response to the Hib component from studies 015 and 012. The level achieving anti-PRP responses greater than or equal to 0.15 micrograms per Ml were 99 to one hundred percent for all groups, and 88 to 95 percent achieving anti-PRP responses greater than or equal to one. The anti-PRP GMTs were between 5 and 7.

As was mentioned earlier there were no data submitted with the license application on concurrent administration of the combination with Prevnar. It should be noted that Prevnar, again, was not licensed, nor was it commercially available at the time these studies were conducted.

Although there are no data on the concomitant administration of Prevnar with this combination, there was some data included in your

briefing materials that suggested that concurrent administration of Prevnar with two different acellular pertussis vaccines, namely a cell amune, and an Infanrix based combination vaccine, DTPa-IPV vaccine showed a diminished immune response to Pertactin.

Now I will review data submitted to the license application on a fourth dose of Infanrix following the combination.

As was mentioned for proposed study for the combination it is a three dose primary series. Children receiving the primary series would then need a booster of DTPa at 15 to 18 months of age.

The manufacturer has indicated that at this time they are not seeking licensure for a fourth consecutive dose of DTPa-HepB-IPV. And these data were not reviewed, formally, as part of this file.

Note that a fourth consecutive dose of this combination would mean an extra dose of IPV, and an extra dose of hepatitis B vaccine. In addition if a birth dose of hepatitis B vaccine is administered it would mean two extra doses of hepatitis B vaccine.

These studies conducted data on a fourth dose of Infanrix following a primary series of the combination. Study 015B was the booster phase to study 015 presented earlier.

Study 028 and study 061, specifically 061 was the booster phase to study 044 that was addressed earlier. Some of these studies, as was mentioned earlier today, evaluated fourth consecutive dose of the combination.

The numbers presented here are just for the Infanrix booster following a primary series. Study 015 received a combination plus Hib in the primary series include four received separately administered vaccines.

In study 015B all children were boosted with Infanrix. In this small study the safety and immunogenicity of Infanrix as a target booster following a primary series of the DTPa-HepB-IPV combination was comparable to the safety and immunogenicity following a primary series of separately administered Infanrix, hepatitis B, and oral polio vaccine.

To summarize the data submitted in support of licensure, all pre-specified immunologic endpoints for demonstrating non-inferiority of the DTPa-HepB-IPV were met, with the exception of the percent responders to FHA.

To summarize the data submitted in support of safety, there was an increase incidence of fever

greater than 38 degrees centigrade in infants receiving the combination compared with the separately administered vaccines.

The incidence of fever greater than 39.5 degrees was not significantly increased. An increased incidence of redness and swelling was observed in infants receiving the combination compared with the separately administered vaccines, but only in the larger study was this difference statistically significant.

Next slide. I would like to acknowledge the individuals that contributed to the clinical review, especially Theresa Fin, and the others listed here, as well as the CBER Review Committee evaluating the product.

I'm going to move on here to present the questions. The first question pertains to efficacy or immunogenicity, are the available data adequate to support the efficacy of the DTPa-HepB-IPV vaccine, when given to infants in a primary series at 2, 4, and 6 months of age. If the data are not adequate to address efficacy what additional information should be requested.

The following questions pertain to safety. Are the available data adequate to demonstrate the

safety of the DTPa-HepB-IPV vaccine combination when given in a primary series at 2, 4, and 6 months of age. Please comment on the increased rates of fever. If these data are not adequate to demonstrate safety, what additional information should be requested.

The discussion point number 3, please discuss data submitted in support of concurrent administration of other routinely recommended childhood immunizations with the combination in infants, namely Hib vaccine, and the 7-valent pneumococcal conjugate vaccine, Prevnar.

Discussion point number 4, please identify any issues that should be addressed in post-licensure studies of this combination, specifically, please include a discussion on the safety and immunogenicity of concurrent administration of other routinely recommended vaccines, namely Prevnar, the safety and immunogenicity of a fourth and fifth dose of Infanrix, following a primary series of this combination, the safety and the immunogenicity of the combination following a complete or partial series of Infanrix, or other DTPa vaccine, and finally the safety of a primary series of the combination following a birth dose of hepatitis B vaccine.

I think I will end here, and I will be

happy to answer any questions.

CHAIRMAN DAUM: Okay, thank you very much, Dr. Ball. I think I'm going to ask the Committee for questions and comments about the sort of the meat of Dr. Ball's presentation. And we will deal with the questions after lunch.

So let's take comments. I see Ms. Fisher first. Why don't you go ahead and start?

MS. LOE FISHER: May I ask a question?

CHAIRMAN DAUM: Yes, please.

MS. LOE FISHER: Earlier when I asked the manufacturer about seizures in this study, it was my understanding that there was one febrile seizure, and it was judged to be due -- the child had an underlying seizure disorder and resulted in the death.

You mentioned, it went by so fast, but seven seizures, five of which were afebrile. Now, what is it, one seizure, seven seizures, how many seizures?

DR. BALL: I think it should be clarified. I think what was referred to was the two seizures that occurred within the seven day time frame after vaccination.

The first slide that I presented, I'm sorry, I can't pull that out for you right at the

moment, referred to seizures that occurred during the whole vaccination course.

It could have occurred six weeks later, you know, three weeks later after the vaccination.

MS. LOE FISHER: I really think we should have more information about the seizure picture, particularly the afebrile seizures.

DR. BALL: I'm sorry, what more information would you like?

MS. LOE FISHER: How soon after did these occur, was it the first time that it occurred in the child, did the child have a pre-existing seizure history, some more information about seizures.

And I have one more question, and then I won't ask another question.

CHAIRMAN DAUM: Well, before you go on to another question, is this information available?

DR. BALL: I think it is available, but I think the manufacturer could probably clarify or expand on the information that I have at the tip of my fingers, which is that seizures were evaluated over the full study course, and that was the first slide on the serious AEs that I presented.

In addition seizures were presented, also, within seven days of vaccination. There were two

episodes of seizures within the seven day time frame. And I think that perhaps the manufacturer would want to clarify further regarding the timing after vaccination, and whether or not there was an underlying condition.

I think that infants -- my understanding was that pre-existing conditions, pre-existing seizure disorders would have kept the children out of this study.

MS. LOE FISHER: Just one other one. Nearly 5,000 of the 7,000 children came from Germany, which unlike the U.S. has a generally homogenous population with respect to genetic diversity.

And also the German children began their vaccinations at 12 weeks, rather than 8 weeks. Can you comment on the possible significance of this, when we apply this vaccine to the U.S. population?

DR. BALL: Certainly. I think that that was something that we looked at very closely, and with regard to the timing of immunization I think that the manufacturer may be able to bring up a slide.

It is in my briefing material that was presented to you that looked at the timing of each dose, and the overlap between the different doses.

And there was significant overlap,

particularly for the second, and somewhat the third dose. The timing, certainly for the third dose was delayed between the infants in Germany versus the infants in the U.S.

So the question that we could readily answer is whether or not the incidence of fever, which I think we've sort of identified as one of the key focal points, did the incidence of fever differ whether the vaccines were given at 2, 4, and 6 months of age, versus 3, 4, and 5 months of age.

I think where this becomes clinically relevant, particularly to parents, and physicians who care for infants, is whether or not that fever that would occur maybe in a 6 week old to a 2 month old, would translate to more hospitalizations, sepsis workups and so on, than perhaps if the immunization is given at 3 months of age.

And I did show a slide that compared the rate of fever between the two schedules, 2, 4, and 6, and 3, 4 and 5, and the rate of any fever was remarkably similar between the two groups.

MS. LOE FISHER: It also could have an effect on death, and seizures, etcetera. I mean, the 8 weeks versus the 12 weeks starting.

DR. BALL: Do you mean in terms of the

occurrence of febrile seizures?

MS. LOE FISHER: Or afebrile. In other words, the one month difference is going to have an impact, could potentially have an impact, both on immunogenicity as well as reactions.

Just because 5,000, almost 5,000 of the 7,000 children came from Germany, and had the schedule, and were not genetically diverse like we are, I think is an important point to --

DR. BALL: I acknowledge that point, and I think that we looked at that as well.

MS. LOE FISHER: Thank you.

CHAIRMAN DAUM: Other comments? I would like to ask a question that is along the similar kind of lines, and maybe we know, and maybe we don't.

But I'm trying to gauge, in my mind, the impact of the fever excess in the combination group. And I saw some data on hospitalizations this morning, and they were reassuring.

But you mentioned septic workup. I don't know what is the standard of care practice in Germany, where most of these children were. But in the U.S. we tend to do probably an excess, but we do a lot of septic workups in very young infants who are febrile.

We hospitalize them, and I get a sense

that there wasn't an excess of hospitalizations. But what did German pediatricians do? I mean, do they react the same way we do?

DR. BALL: I think I will defer to the manufacturer to answer that question.

CHAIRMAN DAUM: Because otherwise we have to know how to interpret the fact that there were or were not an excess of septic workups in the combination group.

DR. KAUFHOLD: In general German pediatricians, the clinical practice that German pediatricians apply is very similar to what is applied in the U.S.

So -- and this includes a very high sensitivity of hospitalizations for sepsis workup. So we don't see a difference between the U.S. and Germany in this respect.

CHAIRMAN DAUM: Thank you. Dr. Gerber, then Dr. Kohl.

DR. GERBER: Could I just follow up on that? Was there an analysis done of just U.S. infants in terms of hospitalization rates, and septic workups between the combination group and the other group?

I believe all of the comments that have been made so far have been on the combined German-U.S.

group.

DR. KAUFHOLD: Yes. A similar analysis has been done for the comparative study 015, and there were no differences between groups.

CHAIRMAN DAUM: Dr. Kohl?

DR. BALL: I think it should also be noted that, you know, the sample size is different between the two studies.

CHAIRMAN DAUM: Smaller. Thank you. Dr. Kohl, please.

DR. KOHL: I want to reinforce Ms. Fisher's point with what I see as a ten percent rate of fever greater than 101.5 in the combination group, versus a five percent rate in the separate immunization group.

And I honestly don't know enough about U.S. practices. But if you have a four or five week old with a 101.5, you are talking about a febrile neonate.

And that pretty much triggers the into the hospital sepsis work. Maybe Dr. Faggett can help us these days with what is going on in the real world out there.

DR. FAGGETT: I would be very concerned with the managed care impact you would have fewer

hospitalizations in the U.S. than Germany. I would submit that that would be my inkling. I don't have the figures, but I think that we have to look at it in context of limited hospitalizations here, recently.

CHAIRMAN DAUM: Dr. Stephens?

DR. FAGGETT: Let me, while I have the mike, I think this speaks to the whole point that was brought up about small sample size as well. I think as a general comment I'm very concerned about small sample size, here, 200 U.S. children compared to 500, etcetera.

CHAIRMAN DAUM: Dr. Stephens, please.

DR. STEPHENS: My questions are on a different subject, and that is the interference with immunogenicity questions that arise, to some degree, with the pertussis.

My specific question has to do with the Hib data. And at least in some of the other studies, that I think you gave us as part of the handout, there was some evidence that the levels achieved against anti-PRP for one were less.

Do you recall those data?

DR. BALL: I'm sorry, for one what?

DR. STEPHENS: For one microgram.

DR. BALL: One microgram.

DR. STEPHENS: Yes, the one microgram levels for anti-PRP were somewhat less, as I recall, in some of the other studies. I think 17 was one of them. Do you remember that issue?

DR. BALL: Well, I can't speak to, on the specifics. But I think that the PRP, while looked at, was considered a secondary endpoint, and with regard to statistical significance, there wasn't as much emphasis to looking at a pre-specified limit of non-inferiority for the PRP response.

But I think that the GMTs across the study are reassuring.

DR. STEPHENS: Can you also comment, further, on the Prevnar? I realize that is not data related to this particular product, but it is troublesome in terms of the -- I think it is Pertactin, low levels with Pertactin with Prevnar.

DR. BALL: Right, and that information was presented in the briefing materials, and it is basically to highlight, I think that the underlying concept is that we don't have data with Prevnar, and so we don't really know what the effect of administration of this combination would be with concomitant Prevnar.

Although it should also be noted that the

same thing is holding true with infants that are given Prevnar in the U.S., and some of the acellular pertussis vaccines that are -- for which we don't have specific data on, say, the Pertactin immune response.

And so then getting to your other point with regard to the interference that was observed, there were -- basically there were two vaccines that we have some information on, Acel-Imune, which was a part of the whole licensure package, and that information is in the package insert for Prevnar, where diminished immune response to the Pertactin component was observed.

In addition there, as part of a post-licensure commitment on the part of Wyeth Lederle, a study in Germany was performed using an Infanrix based combination, DTPa-IPV mixed with HIb, not the specific combination in question here today.

And, again, with this particular vaccine, a diminished immune response to the Pertactin component was observed.

I think I also would defer to any specific comments from my colleagues in the Pertussis labs, Theresa Finn, with regard to what the potential clinical relevance of the observed immune response difference is.

CHAIRMAN DAUM: Dr. Finn, do you care to make a response?

DR. FINN: With respect to the pertussis components I think that the data that the manufacturer has presented on study 027, which was the exact same lots in a larger study, and there was also in that study a separate administration arm.

I think that that study met all pre-specified endpoints with respect to percent responders to all pertussis antigens, and GMTs to the P-antigens. And also for lot-to-lot consistency, as well as comparison to the separate administration vaccines, which included Infanrix.

CHAIRMAN DAUM: Thank you. Dr. Ball, I have a question for you.

I was thinking, reflecting on some of the comments that were made about the German subjects, and the lack of ethnic diversity among them.

But I recall seeing something in the briefing materials we were sent for this meeting that in the U.S. subjects there wasn't that much ethnic diversity, either.

And I wonder if you would comment, from FDA's perspective, about what you asked for, and how you guide manufacturers in preparing for a meeting

like this in terms of enrolling individuals of multi-ethnic groups, and are there any requirements being set there, and what are we doing to ensure that everybody participates in these trials?

DR. BALL: I think with regard to your first point, I just wanted to clarify that there was one study in the U.S. that did have, you know, a broader diversity of the study population.

And so it is possible, I think, particularly in the U.S., to gather those data. I think that I might defer to Dr. Midthun in terms of any specific requirements. I'm not aware that there is any regulations that indicated, with regard to racial makeup of the participants, what that should be for clinical trials.

DR. MIDTHUN: I think obviously that -- is this on?

CHAIRMAN DAUM: Come to the table up here.

DR. MIDTHUN: Obviously we always encourage diversity, and also there are guidelines that also speak to having, you know, gender presentation also, to make sure that one has a broad group, that one has encompassed.

But with regard to any specific types of numbers, I'm not aware that there are any. But,

obviously, we always look for diversity and for gender representation.

CHAIRMAN DAUM: More comments? Dr. Griffin, please, Dr. Fleming next.

DR. GRIFFIN: Could I just clarify what is proposed here, from a broader perspective, with respect to hepatitis B?

It is my understanding that the current recommendations are for immunization at 0, 1, and 6 months in the U.S., and some of that is based on the thought that there is significant amount of transmission that may be occurring peri-natally, or in the early time of infancy.

So is the proposal here that you would continue to give that dose at birth, and then add 2, 4, and 5? I just don't understand how this would fit.

DR. BALL: I think we have Dr. Wharton that can clarify any remarks I made. There is not a recommendation for a preferred dose at birth. It is my understanding that it is basically, and if you look at the immunization schedule that I put up, there is a range, it is from zero to 2 months of age.

And so I think that we asked for data on this vaccine after a birth dose, recognizing that a large proportion of infants in the U.S. do receive a

birth dose, and that there may be some public health reasons.

I also wanted to clarify that, you know, in terms of the FDA review, we evaluate the proposed indication, which is 2, 4, 6 months of age. Vaccine recommendations are made by Advisory Committees such as ACIP, or the AAP Red Book.

CHAIRMAN DAUM: Dr. Wharton, do you want to comment on this very issue, birth dose?

DR. WHARTON: Yes. Just to emphasize what Leslie said. The ACIP recommendations incorporate lots of flexibility, and do not at present indicate a preference for the birth dose.

And clearly it is a good thing to do in many settings, where there is mothers in whom screening has not been performed, and results are not available at the time of birth.

But I don't expect as the ACIP recommendations for hepatitis B vaccine are revised, that there will be a preference for the birth dose, although it is a good idea in many settings to deliver it.

CHAIRMAN DAUM: And I guess before I call on Dr. Fleming I can't resist one comment, and that is that the CDC investigators, as well as people from our

group in Chicago, have shown that birth dose administration does, depending on how you slice and add, make it more likely that you will be caught up to date in your hepatitis B series, and in our study it looked like it was more likely that you would be caught up to date in all the series by the time you were two years old.

So there was, beyond the scope of this meeting, and not an issue for us to delve into, probably, further here, because it is a policy committee issue, but there is some benefit to the first dose, perhaps unexpectedly, perhaps by bonding with mothers at birth.

DR. WHARTON: And just to amplify, I think a related issue has to do with the complexity of the childhood immunization schedule, and the current necessity of delivering a large number of injections at the 2, 4, and 6 month visit, in the absence of much choice in the way of licensed combination vaccines.

And, clearly, administering the first, and even the second dose of hepatitis B vaccine prior to the two month immunization visit, is one way to avoid having to deliver so many injections in those early visits, at 2, and 4 months of age.

CHAIRMAN DAUM: Dr. Fleming. Thank you,

Dr. Wharton. Dr. Fleming, Dr. Kohl, and Dr. Diaz.

DR. FLEMING: I think I will defer until after lunch most of the discussions of a lot of issues that are perplexing, from my perspective, on the immunogenicity analysis and the non-inferiority, specific non-inferiority analysis of that.

But there is one element with Dr. Ball here I would like to address. And that is, the real essence of the information on the immunogenicity is in 015, the most important data, group 1 and group 4.

And it is very noteworthy that that is based on 100 people in each group. And I would like to discuss, after lunch, how we have come up with these margins, and a lot of the controversies about those margins.

But putting that discussion aside, and saying we believe that they make sense, essentially if you have 2, or 3, or 4 people that fail to achieve the threshold target for any of these antigens, then essentially you are not going to hit the non-inferiority margin.

My understanding is we have 100 people per arm. And yet if we look, for colleagues that have the FDA briefing document, your briefing document, on page 16 you give us a very key table.

And there are some columns in there that we have largely ignored in all of the discussion today, and those are the ns. The ns here aren't 100 and 100. The ns here are around 90 in group 1, and in the 70s in group 4.

That is leaving a lot of people out of the analysis in settings in which 2 or 3 people failing to achieve targeted levels yields failure to achieve a non-inferiority.

Where are all those people?

DR. BALL: You mean the difference between the initial end enrolled, and the --

DR. FLEMING: The only number that I've heard referred to today, by your presentation, or the sponsor's, indicates we had 100 people per group in those four groups, in 015.

DR. BALL: That would be related to the total cohort, which would be defined, the manufacturer defined as infants that received one dose.

I didn't -- I think that some of this explanation is in the briefing material about how they defined the intent to treat cohort for immunogenicity, as well as according to protocol cohort for immunogenicity.

And so I think that perhaps the

manufacturer can comment further about why there is a discrepancy between the numbers of infants that received the vaccine, versus the number that serology was drawn.

You will recall that serology was drawn after the third dose, so that there is some withdrawals, or other reasons that those information were not obtained from the infants.

I guess I'm trying to see your larger point. I think that it would be a big issue if we saw, maybe I'm misunderstanding where we are going with this, that it would be a big issue if the manufacturer failed to show a non-inferiority.

But for all of the antigens, with the exception of FHA, they did demonstrate non-inferiority. And I think that, you know, your larger point may be with regard to the small sample size.

And I think that, you know, that is acknowledged.

DR. FLEMING: There are two issues. One of them is with the small sample size there is considerable unreliability in these analysis. There is, in fact, a possibility of failing to achieve conclusive evidence of non-inferiority, even though in truth non-inferiority exists.

So, in essence, it may be that for FHA there is truly comparable levels of achieving the threshold targets, but in small numbers here it was entirely possible that you would see one, or two, or three cases that didn't, and that would be enough evidence to not carry you to the threshold.

Now, my argument there is that is the price the sponsor pays for having done a study that is really too small to be able to asses, conclusively, whether there is non-inferiority.

But the other question is very different, which was really the essence of what I was trying to get at here, is any one of these measures, any one of these ten antigens, if two or three, or four of those people in the 100, in group 1, that didn't get included in your analysis, in essence, didn't achieve a level of protection that was, in fact, related to their being randomized to this combination vaccine, it would have led to a conclusion of non-inferiority.

So because of the striking missingness here, all of this data are actually still consistent with non-inferiority, unless you can give me, in essence, a fairly ironclad argument that the people that aren't in these analysis are, in essence, just randomly eliminated, and not systematically different

from the people that are in this analysis.

DR. BALL: Yes. I think the proper person to answer this is Dr. Howe.

DR. HOWE: So in general the main reason for elimination from the ATP analysis was lack of compliance to either the vaccination schedule, or the blood sampling schedule, which could definitely impact on the immunogenicity.

In addition, in looking at the table that you are referring to, I believe that in some cases the low n is just based on volume limitations, for instance, for the polio assays there is a large volume necessary to run those three assays.

And because the response rate is expected to be very high we set up a prioritization on what antigens should be run when. And they were in the lower priority. So it is really based on volume consideration, it is not that we had a result we threw away.

DR. FLEMING: But this is really confirming that this is an issue of concern. Actually it may be a bias against the product here, but I don't know for sure.

At least the reason I would be hopeful it is a bias against the product, hence we are actually

confident that the result is more convincing than what we are seeing, is the fact that we are missing about ten percent of group one, and twenty to twenty-five percent of group four.

But what you said, a lot of these people are missing because of issues that relate to non-adherence. And, in fact, in the real world if I have a vaccine that twenty percent of the people can't adhere to, and as a result I don't achieve levels of seroprotection, that is a non-achievement of seroprotection levels.

That is just as important as when I don't achieve seroprotection in somebody that I do administer the vaccine to. And so those of us who believe in intention to treat believe in it not because it is the way to keep an analysis unbiased, but it reflects the real world.

I want to know, with this strategy, what percent of my infants will be protected. And if an infant is non-adherent, that is part of the failure to achieve protection.

At least here I'm a little bit reassured that there are more people who appear to be non-adherent to group 4 than group 1.

But if I were at the FDA I would nail this

down and try to understand, exactly, what is going on here. Because it has a lot to do with interpreting the reliability of these conclusions as to whether you have non-inferiority.

CHAIRMAN DAUM: Thank you, Dr. Fleming. Dr. Kohl?

DR. KOHL: I wanted to get back to the seizure question in the briefing data. Again, we have seven seizures in the combined group, and we have zero seizures on a much smaller number, but zero seizures in the control, if you will.

And Dr. Fleming can probably help me here. When you have zero in the control, then you don't know if it is zero, or some much larger number. Please remind us somebody, and there are enough people in the audience who would know this, what the expected rate of seizures are at this age, or after these series of immunizations, just to put this in perspective.

But, again, it gets back to the question of not having enough numbers. We don't have enough numbers to tell whether there is a significantly increased incidence of seizures due to this vaccine.

DR. BALL: I think in terms of, you know, I think that we acknowledged that, and that was part of the point concerning the slide.

CHAIRMAN DAUM: Thank you. Dr. Diaz next, and Dr. Goldberg, and then we are going to take a break.

DR. DIAZ: I just had a comment that goes back to the schedule, the preferred schedule. And just make the comment that the children that we are dealing with in these studies, there is no real preferred, and 2, 4, 6 is adequate, but we have no data. And I think they were intentionally excluded, any child who was born to a HepB surface antigen positive mother. In that setting there is a preferred birth dose.

DR. BALL: Right.

CHAIRMAN DAUM: Thank you.

DR. BALL: Thank you for that clarification.

CHAIRMAN DAUM: Dr. Goldberg?

DR. GOLDBERG: Just to follow for a minute on what Dr. Fleming raised. Can someone, either the sponsor or you, just present for the group 1 and group 4 data in 015, the number of infants that had each dose in the schedule?

DR. BALL: I think that someone had this data.

DR. GOLDBERG: Someone should have that,

and I think that would inform the discussion with regard to the meaning of that, the missingness.

DR. BALL: You mean the attrition rates between --

DR. GOLDBERG: How many, you know, what proportion of infants had dose 1, dose 2, dose 3 by group.

DR. KAHN: We can share this data, but we would ask if we could share it right after lunch.

DR. GOLDBERG: That is fine.

CHAIRMAN DAUM: Thank you. Okay, I think we've come to the point where we thank Dr. Ball for the presentation from the FDA.

It is 12:35, we will take a one hour lunch break, and reassemble at 1:45. Thank you very much.

(Whereupon, at 12:48 p.m. the above-entitled matter was recessed for lunch.)

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

(1:55 p.m.)

CHAIRMAN DAUM: Could we come to order please?

Good afternoon. The first agenda item for the afternoon is an open Public Hearing. There are several potential speakers, by my list here and while the are thinking about whether they want to speak we have in absentia, a letter to read from Dr. Peter Hotez as part of the open Public Hearing. Ms. Cherry will read it.

MS. CHERRY: Dr. Hotez had planned to speak today, but when he couldn't, he sent this and asked me to read it.

It's the statement of H.R. Shepherd, Chairman, Albert B. Sabine Vaccine Institute. The Albert B. Sabine Vaccine Institute eagerly anticipates U.S. approval for the new pentavalent vaccine that will protect children from five very serious diseases. Diphtheria, Tetanus, Pertussis, Hepatitis B and Polio.

By combining five vaccines into one, it will cut from nine to three the number of shots needed to get protection from five diseases. I am sure American children and their parents will join me in welcoming this development. Immunization is the

cornerstone of disease prevention.

Thanks to mass vaccination, once commonplace deadly diseases such as polio, measles, meningitis, tetanus and pertussis are extraordinarily rare in the U.S. But disease prevention requires continuing immunization which combination vaccines make easier.

Combination vaccines make it easier for parents and children to comply with school vaccination requirements, by reducing the number of trips to the doctor's office and slashing the number of shots kids must get. They make it easier for health care providers to keep up with their young patient's vaccinations, by simplifying the immunization schedule. And that's it.

CHAIRMAN DAUM: Thank you, Ms. Cherry and Dr. Hotez wherever you are. Is there anyone else that would like to speak at this open Public Hearing? Dr. Peggy Reynolds.

DR. REYNOLDS: Margaret Reynolds, University of Maryland. I'm the Red Book representative to this meeting, but the comments I'm going to say are simply mine and not representing the Red Book.

I should mention that I do vaccine trials

with Merck, GlaxoSmith Kline, although I have never had any involvement with this vaccine or any of its components, Aventis Pasteur and Wyeth-Lederle.

Because there, most the Committee members are not clinical pediatricians, I wanted to, to comment on the really very pressing need for combination vaccines in the country at this time, so that you can, you can, you can think about this vaccine in the context of the current public health situation in the U.S.

And that is, from my perspective, that, in a sense, we're drowning from our own success. There have been six new injectable vaccines introduced in the last ten years.

That in 1995 children by two years of age received five injections. They now receive twenty. And I think this is contributing greatly to the anxiety and fear about immunizations in this country.

Is it no wonder that twenty-five percent of parents think their children's immune systems are being overwhelmed and fourteen percent would opt out of some vaccinations.

I think if you went to an internist and they told you in the next two years I'm going to give you twenty immunizations, would think that was fairly

strange.

Also having to give a fifth immunization was the last straw on the camel's back for many primary care physicians. Instead of doing that, instead they're putting off IPV, they're putting off hepatitis B. Some are bringing the children back every month and that's a recipe for diminished immunizations.

And one final point that I think probably many of you hadn't thought about but because of the number of injections, it has become exceedingly difficult to recruit children into pediatric vaccine trials.

Because very few parents are going to want to subject their children to yet more immunizations and blood draws and this is at a time that you want more safety information and not fewer.

And I'm, I fear that until we get combination vaccines, the only people who are going to be successfully able to recruit into trials are the contract research organizations where pediatricians are enrolling their own patients. And I fear that the academic investigators may be driven out of business in this current climate.

One last thing and that's that it really

hasn't been brought out, the relative importance of FHA versus PT versus pertactin. And I think those who study the serologic immune response and serologic correlation to protection to pertussis would agree that FHA is probably the least important antibody in affording protection. That's it.

CHAIRMAN DAUM: Dr. Reynolds, we thank you for taking the time to address us.

Is there anyone else who would like to speak at the open Public Hearing?

(No response.)

CHAIRMAN DAUM: Okay. In that case we're going to move on to the following sequence. First, we will ask Dr. Taffs to remind us regarding, that sounded like the cell phone.

Could I ask again, please slap the wrists of my colleague Dr. Faggett and ask again that people please don't ring your cell phones in here. It's very distracting. So Dr. Taffs will reacquaint us with the questions as they were modified. And please pay attention to this version of them.

Then the sponsor has asked to show a couple of slides that will clarify some of the discussion items this morning. I believe there's three of them and we're going to allow that.

And then we're going to ask Dr. Fleming to begin the discussion, which at first can be general as far as I'm concerned.

And then after awhile I would ask that we focus it towards the questions themselves so that we can give the FDA the input that they need from us this afternoon. So, we'll go ahead now with Dr. Taffs and the four questions.

DR. TAFFS: Thank you. I would like to repeat my request, on behalf of the Center for Biologics Evaluation and Research, that the Committee assembled here today consider a series of questions and discussion points and provide their commentary and their recommendations regarding this vaccine.

On question number one, which is a voting question, are the available data adequate to support the efficacy of DTPa-HepB-IPV vaccine when given to infants in a primary series at 2, 4, and 6 months of age. If the data are not adequate to address efficacy, what additional information should be requested?

Discussion point two. Please discuss whether available clinical data are adequate to demonstrate the safety of the DTPa-HepB-IPV combination vaccine when given to infants in a primary

series of 2, 4 and 6 months of age. Please comment on the increased rates of fever.

If the data are not adequate to demonstrate safety, what additional information should be requested?

Discussion point number three. Please discuss the data submitted in support of the concurrent administration of other routinely recommended childhood immunizations with the DTPa-HepB-IPV vaccine in infants. That is Haemophilus influenza Type B vaccine and 7-valent pneumococcal conjugate vaccine, Prevnar.

The final discussion point to consider, please identify any issues that should be addressed in post-licensure studies. Specifically, please include a discussion of the safety and immunogenicity of concurrent administration of other routinely-recommended vaccines. For example, Prevnar.

Safety and immunogenicity of fourth and fifth dose of Infanrix DTPa following a primary series of DTPa-HepB-IPV. Safety and immunogenicity of DTPa-HepB-IPV following a complete, or partial, primary series of Infanrix or other DTPa vaccine.

And finally, safety of a primary series of DTPa-HepB-IPV, following a birth dose of hepatitis B

vaccine.

CHAIRMAN DAUM: Thank you, Dr. Taffs for reacquainting us with the issues at hand. We'll now call on Dr. Howe to show a maximum of three slides.

DR. HOWE: Actually, before you show the first slide, I just wanted to get back with the answer to the question about the attrition rate, I guess. Or the information about how many children received each dose of vaccine in Study 015, the U.S. Study.

And if we looked at the data for group one who received the combination Infanrix HepB-IPV, a hundred children received the first dose, ninety-six received the second dose and ninety-five received the third dose.

In group four, the separate administration, a hundred received the first dose, eighty-seven the second dose and eighty-four the third dose. So there was a higher attrition rate in the group that received separate injections.

The slides that I wanted to show you now are basically to help answer the question about the clinical relevance of FHA and the fact that the FHA was, for the vaccine response rate to FHA anyway in the 015 Study, was, was not found to be statistically non-inferior to separate injection DTPa.

So this is just a series of the three RCCs looking at each pertussis antigen, comparing the results from Infanrix HepB-IPV vaccinated children in Study 015 to data from our household contacts study conducted in Germany and with sera run in the same lab in order to make the comparison valid.

And the black line here is, the black curve is data from Infanrix HepB-IPV vaccinated individuals in Study 015. And the two lines here, as was alluded to earlier, multiple lots of vaccine were used in the household contacts study in Germany.

So we have data for the most immunogenic lot in red and the least immunogenic lot in yellow, for each antigen. And you can see that for anti-PT, obviously Infanrix HepB-IPV was at least as immunogenic, actually a little bit more, the curve is to the right.

Here are the results for anti-FHA. Again Infanrix HepB-IPV vaccinated and most and least immunogenic lots for the household contacts study. And here are the results for anti-pertactin. The curve for anti-pertactin fell largely in between the most and least immunogenic lots.

So based on these results, we don't feel that there is any, that the lack, ability to show non-

inferiority for FHA has any clinical relevance.

The other question I'd hoped I might shed a little bit of light or maybe help put in perspective was the question about the rates of seizures in this age group.

And what we did is, we went back and looked at the package insert for Infanrix and from that package insert we have rates of febrile seizures and afebrile seizures. For Febrile seizures there were actually none. And this is data from the large household contacts study which was the largest self-contained study for afebrile seizures, 0.13, and that's per thousand doses.

If we then take the same type of approach and look at the largest self-contained study in the Infanrix HepB-IPV file. The rate of Febrile seizures within seven days was 0.07 per thousand doses and for afebrile seizures again 0.07 per thousand doses.

So the rate is comparable to that in the Infanrix package insert and lower than that for historical data following whole cell vaccine.

The last comment that I wanted to make was with respect to the overall safety database, because there was a question about the n of 7000 and the fact that that seemed small I guess to some people in the

room.

I think the reason for that is because what we're talking about here is a combination vaccine that is made up of individual components that are already licensed in the U.S. in the case of DTPa and the hepatitis B and similar to U.S.-licensed product in the case of IPV and each of those individual components has its own well-established safety profile and in point of fact the safety trial that we did in Germany was powered for safety.

We specifically did that study to look at safety. And what we found was, and the only thing that we found was a higher rate of low-grade fever. Based on that, the question was what's the clinical relevance of the low-grade fever and carefully looking at all the data and looking at things such as sepsis work up, hospitalization with fever, antipyretic use, duration of fever, Febrile seizures, we believe that there are, that there is no clinically-relevant consequences of the high or low-grade fever that was seen in the study.

CHAIRMAN DAUM: Thank you, Dr. Howe.

What we'll do now is have, try and get a sense of how many general comments Committee members might wish to make. We'll start with Dr. Fleming.

And then we'll see who else wants to talk, generally, and then, once we get a sense of where that's going, we'll start focusing on the individual questions themselves, beginning with our sole voting question, which is question one.

So Dr. Fleming, may I turn the floor over to you, please?

DR. FLEMING: All right. Thank you. I think what I will actually do is just focus my comments on those that relate to the immunogenicity or inefficacy issues and I'll wait for us later in the meeting to come to the safety issues.

The issues that I wanted to raise here, let me just preface what I'm saying to clarify that the issues that I'm raising don't lead me to the conclusion that the combination vaccine is inferior in its efficacy profile, but rather, that I'm, I'm left with a lot of uncertainty about whether there's adequate evidence here to establish non-inferiority as we have set this criteria.

The essence of the data, as I see it for this, is from in essence, the 015 trial, with some relevant information from 044 and 030.

Let me also preface my comments to say that I am well aware that doing a full-fledged

efficacy trial, that would actually be able to document non-inferiority in actual cases of disease, would be a very high standard to expect.

At the same time, there are, there are levels of differences in complexity when we are trying to rely on a immunogenicity surrogate. If we were looking at lot-to-lot variability, it's the standard that we would use immunogenicity surrogates.

I just point out here, there are a number of specific challenges that I would argue should lead us to wanting to have a fairly rigorous establishment of immunogenicity and those issues are, on the one hand we're looking at a combination vaccine and trying to address whether or not the actual biological process associated with delivering these vaccines in combination, would alter their immunogenicity and, in turn, their ultimate efficacy.

We also have, one of the components here, is an unlicensed component. The IPV component is unlicensed, which I would think should lead us to an additional level of rigor as we make this efficacy assessment.

And thirdly, the HepB is being administered in a different schedule than what has been the tradition. Not to mention that there still

remain these issues of lot series and lot-to-lot variability.

So when I think about all of this it strikes me that this is a setting where we should be particularly rigorous in our assessment of whether there's adequate evidence of immunogenicity to make it plausible that efficacy is maintained.

Having said that, the way that this has been approached by the sponsor for the non-pertussis components, is to essentially identify an assay cut off, or what I might call a potential threshold, and look at the percent of infants that achieve antibody titers above that threshold. And it's been stated that that threshold, for example, has been arrived at by noting its correlation with immune protection.

So these thresholds might be the 0.1 international units for the diphtheria and tetanus and for the HepB it's ten milli International Units.

I guess, to my way of thinking, it is always important to step back and remember that even if we see in large data sets correlations between achieving certain antibody titers and rates of infection, it is important to remember that levels of immune response are undoubtedly a continuum and levels of protection would presumably be enhanced as you

achieve more complete immune responses on those particular components that are really causal.

And this is always an incredibly difficult issue to sort out. Undoubtedly a vaccine will generate a myriad of different immune responses and really, fully understanding the essence of which of them are really causal is probably a task that would never be fully achieved. And essentially what we have done is we have dichotomized this myriad of different potential immune responses into looking at whether we see a given assay cut off.

And I just would like to step back and say it's entirely possible that you could have a correlate, and yet that correlate may be a marker for a myriad of other types of immune responses that are carrying a lot of the causal aspect of protection. And so it always makes me very cautious in interpreting these results.

But if we use, for one example, the HepB example, where we're trying to achieve a level of ten, I would challenge the FDA to go back and really be sure that the data are adequate to state that once you achieve a level of ten, that really is a threshold. And that that level is truly adequate to say that we have maintained a high level of protection.

And it's not enough to look at those with less than ten versus those with more than ten. Those with more than ten may be largely people with levels of a thousand. And so we have to be sure that we have a lot of data of people between ten and thirty to be able to say ten is enough to achieve protection.

So having said that as a background, the essence of the data that we have presented to us that's the most reliable here is the direct randomization between the combination of the individual component administration in 015. And as we've already discussed, this is based on a hundred people per arm.

So essentially, the most significant immunogenicity data that we're going to be using to address this complex situation that could lead to administration to tens of hundreds of thousands to millions of infants is based on the comparison in immune responses in a hundred per arm and I've already mentioned one of the issues there is that there's ten to twenty-five percent missing information there as well.

But essentially the primary analysis that's being addressed here is did we achieve a comparable fraction of participants who had this cut

off, this threshold?

And essentially what we're saying here is we're using a weaker standard, and appropriately so, than requiring superiority.

We're not saying that the combination has to have a significantly higher fraction that achieved its cut off, we're saying that it has to be high enough so that you can rule out that you're ten percent less.

Well the first statistical issue I'd like to say about that is if we were trying to show superiority, if we were talking about a combination that was adding an antigen to a standard and you had to show superiority, we would ask that the ninety-five percent confidence interval rule out equality.

We would basically say we want to have, and this is the standard for strength of evidence for superiority, a two and a half percent false positive error rate. The way this has been set up, is we are expecting a weaker standard.

We only have to rule out that we're not ten percent worse. And yet we're allowing a five percent false positive error rate by using ninety percent confidence intervals.

So the first issue I would urge the FDA to

consider here is to move back into the world of standard statistics to say the standard for strength of evidence is a two and a half percent false positive error rate. Meaning that these confidence intervals should be ninety five percent confidence intervals.

Is that irrelevant? Well, it's not at all irrelevant. Because the levels of differences that are consistent with the data are much higher. If we go to the FHA data in 015, we have failed to establish non-inferiority, relative to the seropositivity rate. We also have failed to establish non-inferiority with the GMT if you're using a ninety-five percent confidence interval.

So that data there, in my view, don't prove inferiority, but because of inadequate sample size this year, if one was using a proper statistical approach, they do, though, fail to be strong enough to establish non-inferiority. And that essence is in essence in my view as confirmed by the 044 trial where we're looking at lot-to-lot.

It's quite striking the variability that we have in rates of achieving seropositivity and in the GMT rates for PRN and for FHA.

And, I guess the last issue I'd want to raise, is if the sponsor could put up again the slide.

And it was one that Dr. Howe had shown when she was discussing the 030 data. And specifically it related to trying to address the relevance or importance of the fact that we see about a four-fold reduction in the GMT for HepB in the 030 trial.

In the sponsor's presentations, my big concern with the way we have set up the primary end point is that we have essentially defined the primary end point, achieving the threshold level or assay level for positivity.

And it may well be that that assay level for positivity is lower than what it truly has to be to represent a patient or a participant or an infant that truly has the global level of immune response that renders protection.

PARTICIPANT: Which slide do you want to see?

DR. FLEMING: It's the slide that showed the historical data. Because you put into context with previous studies what the level of GMT would have been for other vaccines.

And it in particular, it contrasted the thousand, this slide, thank you. In this particular study, if I'm following your logic here, you're pointing out that the, whereas the combination vaccine

was one of those orange dots in this trial around a thousand and the other relevant dot is the dot of 3,500 up there under the 016?

DR. HOWE: This is the data from the HepB study itself that I showed you.

DR. FLEMING: Yes.

DR. HOWE: And this is data from any of the Infanrix HepB-IPV studies that were given on a 2, 4 and 6 month schedule. So, all of the orange dots come from Infanrix HepB-IPV studies. One of them would be 015, another would be, I think two of them actually are 044. And the green dot --

DR. FLEMING: So where would the 030, are the 030 dots up here on this? The thousand. And where would the dot be that corresponds to the 3,700 GMT for the comparator group in 030?

DR. HOWE: The comparator group in 030 isn't on here. This is published data from package inserts for the two U.S. licensed products as well as data in the literature for the two vaccines, including Recomavex, two different strengths, on a zero one six-month schedule administered to neonates.

DR. FLEMING: All right. So basically you're not, on this slide we really have no way of trying to put into context the relative difference

we're seeing in the 030 trial. In the 030 trial, this is the data, if I'm working this correctly.

DR. HOWE: Right. If we had plotted the 030 and put it with Engerix 016, it would be closer to this dot, is what you're saying.

DR. FLEMING: Right. Well, and my concern is, if what we're seeing here is, in our comparison IN 030, an average level of response that's one quarter of what we're seeing with the comparator group, but all of this other experience is telling us that rates are much lower than the 3,700, it makes me wonder whether the thousand that we're seeing is an overestimate, i.e., is there something specific to the population that we had in this randomized trial 030.

If we're seeing in our comparator group, we had a level of 3,700, and if your argument is 3,700 is much higher than what you would have expected from prior experience, then my response to that isn't that more than one thousand is fine, but rather the one thousand might also be an overestimate of what you would achieve in a much broader context.

So it's, and probably it's not worth a lot more discussion there. I think the essence of the concern just to summarize as I think through this is that the data that we have that is the most

informative to efficacy, is data on the immune response, specifically provided to us in the 015 trial, with basically on the order of a hundred patients.

And IF we were using statistical procedures with ninety-five confidence intervals, we're essentially seeing, not just for FHA, but for the polio virus types two and three, also some evidence of concern and this is confirmed in the 044 trial with FHA but also with the PRN showing considerable heterogeneity.

DR. HOWE: Can I just respond to the question about the DTPa-HepB and whether or not that would be an overestimate because in, I think the fact that we have multiple studies with Infanrix-HepB-IPV, giving consistent rates of 1,500, you know between 1,400 and 1,600 is one fact.

And actually in one of the studies, which was the 015 Study, we had a head-to-head comparison with the DTPA-HepB-IPV and DPTa-HepB and in point of fact we had a result of 1,600 here and 900 here, confirming the DPTa-HepB results for the GMT. And I think the other important point is that the sera protective cut off is down here.

DR. FLEMING: Well, that's what I'm

trying, I'm trying to press the issue that where you define that seroprotective cut off is a very controversial issue.

And the other point that I'm trying to make here, let me just very quickly make it again, is the most relevant comparison comes from a randomized comparison. Not from what an array of different things would show in natural history. And what we have from a randomized comparison is a four-fold reduction.

CHAIRMAN DAUM: Okay, I'd like to, at this point, thank you, Dr. Fleming, Dr. Howe for commenting, see if the Committee has general comments they'd like to make before we put the first question up and start speaking directly to it. All right, Dr. Kohl.

DR. KOHL: I want to echo Dr. Reynolds comment and I kind of feel a little remiss. I'm a pediatrician. And we desperately need combination vaccines. There is no question about that in my mind.

And I just want to make sure that the Committee realizes that we need combination vaccines that are effective and safe. So keep those two in mind.

CHAIRMAN DAUM: Thank you, Dr. Kohl. I

didn't see other hands up. And so I'm going to ask to have the first question put up on the board again and begin a discussion about this first question and that is to say that the, this is a voting question. It's the only voting question for the afternoon. And it concerns efficacy.

Are the available data adequate to support efficacy of this combination vaccine when given to infants in a 2, 4, 6 regimen.

So I'd like to have discussion about this question and then after we get a sense of people's opinions and where we're going, we'll have a vote about this question. Comments? Ms. Fisher.

MS. LOE FISHER: I'll just do my comments and my vote at the same time, if that's all right. I mean I only have to speak once then.

CHAIRMAN DAUM: It's --

MS. LOE FISHER: Save time.

CHAIRMAN DAUM: Economy is a good thing.

MS. LOE FISHER: My answer is no. That there needs to be a larger trial of this new combination vaccine in the U.S., in genetically diverse populations, with a 2, 4, and 6 month schedule.

And with a longer follow-up period than

fourteen months to assure long-term immunogenicity with all antigens, particularly pertussis and hepatitis B. As well as an attempt to characterize the mechanisms for achieving immunity at the cellular level.

CHAIRMAN DAUM: Okay. We have a vote in and a comment. Other comments? Perhaps we've heard them. Dr. Broome, please.

DR. BROOME: Well, I mean, I appreciate your trying to surface some discussion before we move to voting, because I actually thing that's quite important. I mean I think Tom has raised, you know, perfectly valid points, but I do think they have to be put in the context of what is a reasonable body of data to expect for this kind of product and decision.

I also think it has to be put in the context of you may have one very well designed, randomized trial, but I think with immunogenicity data we've also been comfortable bridging between results from one study and others.

So to characterize this is decision based on one hundred or fewer subjects per arm I don't think is really representative of the data we've seen this morning.

I'm sort of scrambling to pull together

what we do have. And it may be helpful to the Committee to sort of reprise, you know?

Specifically I myself and others have focused on the pertactin and FHA results from 044, but frankly I think we haven't paid enough attention to the fact that there's another consistency lot trial which has 300 subjects per arm in which the non-inferiority is very clear for those antigens, and I find quite convincing.

So I'm not particularly concerned about the possibility of nonequivalence with the FHA or pertactin results. So this is not a very conclusive comment, but just one to say that I think before we vote it's quite important to maybe, you know, reprise the data that bear on the immunogenicity question.

Also I'm really sorry we don't have Stan Lemon or somebody here who could speak more eloquently to the hepatitis surrogate. But my understanding is that's actually quite a good one.

CHAIRMAN DAUM: So, I take it you feel more, substantially more comfortable with these data than previous people that have --

DR. BROOME: Well, I'm flipping through a whole bunch of pieces of paper to try to put the whole thread together. But I, let's just say I don't feel

maybe as pessimistic as the two preceding speakers have.

CHAIRMAN DAUM: I think the, we need to think about this question as what do we believe based on what we heard about the ability of this combination vaccine to protect against the diseases that the individual components protect against.

I mean that's sort of what efficacy's all about. And so, I think that in formulating that idea, do we know enough from the immunogenicity data that were presented this morning, about that to decide the question.

I think that's sort of what we're thinking about here. And I'd like to hear more discussion about whether you think we do know that or whether you think we don't know that and where the gaps are. Dr. Kohl.

DR. KOHL: I'm going to focus on the DTP or the P in particular. And the one piece of data that I was the most concerned about, initially, reading the pre-read and earlier this morning, was the FHA data.

And I think, again, the GMT level, which is all we have with FHA, unfortunately, shows nonequivalency. There's no question about that by the

criterias which may even be weak as Dr. Fleming has mentioned.

On the other hand, we all sat through a very laborious session several months ago looking at a different preparation, and discussing what all this means.

And I think I would have to agree with Dr. Reynolds, which I enjoy doing actually, not would have to, that FHA is probably the least important of the antigens that we know about.

We know that Infanrix itself is quite a good protective vaccine against pertussis and I feel that to hold this up because of one out of three antigens that I don't know exactly what it means, would not be the appropriate thing to do on the basis of pertussis. So I feel, I think comfortable, passing on the pertussis protection from this vaccine.

CHAIRMAN DAUM: Well you want, before we let you put the microphone away, do you want to go a step further and talk about the polio part of the vaccine? Or --

DR. KOHL: Yes. I honestly don't have any problems with the other components of the vaccine. The hepatitis was lower. GMT, again, was lower than the comparator. But the levels are still quite good.

And my understanding is those levels would be quite protective, although that is not my field and I'd love to hear from a hepatitis expert if possible.

CHAIRMAN DAUM: Okay. Other comments? Dr. Diaz, please?

DR. DIAZ: I just have a couple of comments in particular regarding the pertussis and the hepatitis, hepatitis B. I'm not that concerned in regards to pertussis about the FHA, the non-inferiority issues. But, I am still troubled by the lot-to-lot equivalency and immunogenicity results with pertactin.

And I'm not convinced that high maternal antibody accounts completely for those differences in those lot-to-lot variations. The, that coupled with sort of the lack of knowledge, I guess there's a lot of what ifs in my mind.

The data as it stands is reasonable in my mind and yet the what ifs, the issues regarding the lot-to-lot inconsistencies in pertactin, the lack of any knowledge about how this vaccine will behave when given in combination with prevnar, in particular, makes me a little bit uncomfortable and I wish we have more information in regards to that in terms of if there's any cumulative affect along those lines in

decreasing antibody responses to pertactin.

That having been said, likewise I wish we had more information as to just how important pertactin is in the overall scheme of protection. Regarding the hepatitis B issues, I am not overwhelmingly troubled by the differences in the GMTs per se.

And yet, again, the lack of any longer-term data can of regarding the persistence of an antibody response in these subjects leads me to wonder about the overall protectiveness in the long run. Again those are sort of the what ifs that I have in my mind that are a little bit troubling.

CHAIRMAN DAUM: Okay. Again, I think this concept of dissecting in our minds the different components of this as Dr. Kohl and Dr. Diaz have done, it a helpful one. And it may allow you to consider why you do or do not think this is efficacious.

DR. WHARTON: Getting back to the lot-to-lot variation issue, again, if I remember the presentation correctly, although there was nonequivalence in the equivalence testing for the pertactin component, if you look at the reversed hemolytic distribution curves which are provided, they're actually strikingly similar.

Which raised the question in my mind, and I would appreciate someone who's wiser than I to enlighten me on what in fact does nonequivalence mean with such similar reverse cumulative distribution curves. Is the statistical standard that's being applied consistent with what we would consider clinically relevant?

With all the provisos that we don't know what to make of pertussis serology anyway. But they are strikingly similar curves and even the antiprotectant curve, though there's a little bit of daylight between the lines, it's not much, and were I to see these curves in a different context, I would be impressed with their similarity.

The second point is one again which I think has been made that the, that those same lots of vaccine were subsequently used during the second larger study and the confidence intervals were smaller, reflecting the larger sample size, and in fact nonequivalence was not found.

Now granted there was ad mixture with Hib vaccine so it was not exactly the same situation. But, this reassures me, and these consistency issues among the lots I don't find troubling based on these data.

CHAIRMAN DAUM: Thank you very much. Dr. McInnes.

DR. MCINNES: In study 015, comparing groups one and groups four.

CHAIRMAN DAUM: Pam, could I ask you to speak right into the microphone.

DR. MCINNES: Sure. Dr. Howe you gave us the numbers of children who had completed three doses of vaccine in those two groups.

In, there's a delta between those who completed three doses and those there weren't reported and I presumed that revolves they either didn't get a blood draw or they had window violations around the timing of the doses.

And so they're not accounted for in the, according to protocol analysis of the immunogenicity. What do you know about the immunogenicity of those delta children? The children who received three doses and had a blood draw, but had some window violation.

Is it possible to shed some light on them, because I think that addresses something Dr. Fleming raised earlier with if just two or three children had had a different response the impact would have been different on the non-inferiority analysis. So it goes more to the intent-to-treat concept than to, according

to protocol analysis.

CHAIRMAN DAUM: We can ask the manufacturer to comment on that, if they would like to.

DR. HOWE: In terms of the numbers that I just quoted, they were actually just attrition from dose one to dose three, so that wasn't the numbers included in either the ATP or ITT analysis.

It's just the absolute number of children who came for dose one and then subsequently got dose three, whether or not they had blood drawn, sufficient volume were analyzed or what not. So that, the numbers I gave you earlier were simply the number who completed their vaccination.

DR. MCINNES: No. I understand that. For example group four. Eighty-four children received three doses you reported.

DR. HOWE: Yes, that's correct.

DR. MCINNES: The n reported under group four for immunogenicity is a maximum of seventy-eight.

I'm wanting to know if you have data on the six children?

DR. HOWE: So I can tell you their reason for elimination is what you want to know?

DR. MCINNES: Well I want to know if you

have, did you get a blood draw on them, do you have immunogenicity data on those six children. I understand they might have had window violations, which would make them fall --

DR. HOWE: Right. Right.

DR. HOWE: -- outside of the ATP analysis but would be meaningful for understanding the spectrum of immune response, regardless of the window.

CHAIRMAN DAUM: Are there any sera on them?

DR. MCINNES: Yes. Do you have serology on them?

CHAIRMAN DAUM: Are there any antibody data?

DR. HOWE: Yes. I'm just looking at, I have in front of me the ITT analysis which means that if a child had sera available and the assay was run --

DR. MCINNES: Yes.

DR. HOWE: -- and so, do you want this by antigen or per specific, do you want for the pertussis antigens or --

DR. MCINNES: Do you have it for this spectrum of the an, do you have all of it?

DR. HOWE: I do. So again, if we look at a comparison of group one to group four for anti-

diphtheria, it's ninety-eight point nine percent versus a hundred percent. And there would be ninety-two in group one, and seventy-nine in group four.

For anti-T it's a hundred percent and a hundred percent. For anti-PT here we have an n of ninety-three for each of the pertussis antigens and the ITT cohort for group one we have ninety-eight point nine percent, in group one and ninety-eight point seven in group four.

Ninety-five point seven in, for FHA and a hundred percent for group four for FHA. For anti-pertactin, ninety-five point seven versus ninety-one percent, that's group one versus group four.

I just looked quickly at polio. For anti-Hbs the n is ninety-one in group one and seventy-eight in group four, a hundred percent greater or equal to ten milli International Units per ml.

Again for polio one in group one we have an n of 88 with a hundred percent seroprotection. Group four an n of 74 with 98.6. For polio two, 98.9 versus 100 and for polio three 100 versus 100. The same n's as I previously quoted.

CHAIRMAN DAUM: How agile is the Committee with these numbers? We have the technical capability here of putting these on a transparency and showing

them. Would you like to see them that way? Or is Dr. Howe's reading sufficient?

DR. MCINNES: I mean essentially, although I didn't write them all down, the percentage of seroprotection vaccine response is pretty much the same in the intent-to-treat as in the ATP. Is that a fair statement?

DR. HOWE: Yes.

DR. MCINNES: But you add some way between two and four sero values per depending?

CHAIRMAN DAUM: Would you like to have them written down to see them?

DR. MCINNES: No. I don't think so. Dr. Goldberg wanted --

CHAIRMAN DAUM: Dr. Howe would you be willing to take a few minutes and do that? We can banish you to the table to do that. Then we can put them up on the board and they might be easier to digest. Thank you Dr. McInnes. Other comments, queries? Dr. Goldberg?

DR. GOLDBERG: Just to follow this attrition --

CHAIRMAN DAUM: Microphone.

DR. GOLDBERG: Sorry.

CHAIRMAN DAUM: Thanks.

DR. GOLDBERG: Two things. One, to follow this attrition argument, I mean the reasons for the attrition between doses should need to be looked at. I mean are they related to safety events and the intolerability of being able to complete the course of the vaccine? I mean that's key into what the long-term protection from the vaccine would be in the population.

If you're only going to, if you're seriously only going to get the completed course in a differential group of patients. You know and the trick is really to make sure that it's operating the way it is, the way it appears to here which is that a higher percentage are getting the full course of the combination rather than the components.

And that the reasons for noncompliance are not related to outcome in group one like an untoward outcome in group one and annoyance with the vaccine in group, with the number of injections, but no real problems in group four. And I think that needs to be looked at in order to fully evaluate it.

The other point is that there was a discussion about the reverse curves. And I guess I'm not as sanguine that they're totally similar in the sense that what does the small difference in a small

space between the two curves translate to in the large?

I mean we're really talking about vaccines that on a seroprotection basis, whether we like the cut off and we're happy with the definitions, really do a pretty good job in the abstract.

The question is, where they fail. Is that going to magnify in the hundreds of thousands and millions of kids that get this? And so I think we do need to go back to the data if you will and the data about what the levels actually are and I guess I'm concerned about that.

I mean, I'm torn between I think this is a good vaccine, but I'm not fully convinced and totally comfortable and it's these little niggling issues, I mean it's the, you know when you do an adjustment for the maternal levels at baseline. Well, you know, I mean I guess, I'd like, I need to look at that data so that I can see it.

But that's an issue. I mean the assumption's made that well if it's high it's going to stay high and there's nothing you can do. They can't respond.

But if you looked at subjects that achieved a certain level or maintained a certain level

of titer, you could get at that issue. And you could get at it if you stratified by baseline levels. So that there are ways to begin to tease this apart and I think maybe we need to do a little bit of that.

CHAIRMAN DAUM: Thank you. Dr. Meade then Dr. Fleming, Dr. Griffin. Doctor?

DR. MEADE: Yes. Bruce Meade, from the Office of Vaccines at CBER and I'm not going to resolve the niggling issues because they are in fact difficult issues but I think it's important to acknowledge clearly that the cut offs, the values that we come up at cut offs for equivalents for the pertussis antigens are clearly arbitrary.

I mean I think we'd be kidding ourselves if we didn't acknowledge that the values we came up with were arbitrary, hopefully thoughtful, but clearly arbitrary.

And I think the, one of the important considerations as we did obviously what were realistic but I think one of the most important considerations is we were, when we chose what we thought were reasonably conservative criteria for equivalents, for non-inferiority and equivalents, so that when, in fact, differences were observed, we would have a signal, that would identify those that we need to look

at and do exactly the kinds of things you're talking about, that if they are, if you see differences, are these, you can look at, choose which RCDs you want to look at in depth and look at.

And again, I think it's important to differentiate between shifts of an RCDs, you know a small shift, or in fact are you is there a population of individuals that are clearly non-responders. And again trying to put that into context of the value, the information that's available from Fixi trials.

Again, it's, I think we viewed it very much as a signal for which ones we need to look at more carefully. And do the kinds of analysis you're talking about.

And if I could make one more comment, again, in terms of lot consistency issues, I think it's important to recall important issues when we're talking about consistency in manufacturing.

It's a global issue. When we're evaluating consistency in manufacturing, you're looking at a large number of information on the manufacturing, the process, on the characterization and animal and human immunogenicity.

There's no question that the human immunogenicity is important and relevant but it's only

one of the tools we use to look at for evaluating consistency in manufacturing. So it is, again, it's an important issue, but it's not the only issue that's relevant for consistency in manufacturing. Thanks.

CHAIRMAN DAUM: Thank you, Dr. Meade.

DR. GOLDBERG: Can I make another comment?

CHAIRMAN DAUM: If it's very brief, Dr. Goldberg.

DR. GOLDBERG: Very brief. I mean the lot-to-lot consistency vote, speaks to the same inconsistencies, speaks to the same issue.

What does the small difference, if you presume that the immunogenicity is really a surrogate for true efficacy, then a small difference there that goes against the lot that you're using has lower immunogenicity rate. And I may be reversing this.

Translating to potentially lower efficacy which in large here becomes a major issue in numbers. So it's really how close is close enough? And I think that some of that does need to be discussed and agreed upon.

CHAIRMAN DAUM: We're discussing it. Dr. Fleming?

DR. FLEMING: Just to kind of follow up on Judy's clarification and questions that had been

raised about interpreting these data.

If we go to the 044 data and we look at the PRN and we look at the magnitude of the differences, essentially as has been reiterated, we don't have a clear sense of what measure of immunogenicity is a reliable way of addressing efficacy for pertussis.

A best attempt was made. And that best attempt said for this we're going to use the GMT and we want to be able to at least rule out that there could be a fifty percent higher GMT achieved on single administration as opposed to combination. That was what we set up.

Now we didn't observe something that was one-third lower, which corresponds to relative risk of one point five. We observed something that was about a relative risk of one point three, which is part of reason that the curves don't look so obviously separated. But part of the price you pay when you have a small study is that these data are statistically consistent with something more than one point five.

And so the bottom line to that typically is if you do a study and you see a positive trend and it's not significant, you say ah well, it's a positive

trend and if the sample size had been big enough it would be significant, so approve. No you say, that's the price the sponsor has paid for not doing a study of adequate size to reliably understand immunogenicity.

That's in essence what's happening with the lot-to-lot assessment. There is, in fact, unfortunately an estimate that the GMT is lower and it's a variable estimate because it's a little trial and as a result we cannot state with confidence that you might not have a one and a half fold higher GMT in the individual administration.

And then back to Claire's point about the Hep surrogate. The comments that I have raised haven't challenged that the Hep surrogate might not be a good surrogate. That there is a correlation between these antibody levels and protection. The big question is are you capturing the essence of the importance of that surrogate by dichotomizing on whether you achieve a level of ten?

And that would mean you've got to have evidence on a lot of people that have ten to fifteen and show they're protected.

And I strongly suspect we don't have that and I've been probing to see if we do have it and I

haven't yet been convinced that we do.

CHAIRMAN DAUM: I think we do. We're going to ask Dr. Feinstone from the FDA who's just come in to address that very question for us. We produce answers for this Committee. Dr. Feinstone thank you for coming. Feinstone. The recall.

DR. FEINSTONE: We've actually been struggling with this issue of hepatitis B titers for some time. Going back to the original plasma dry vaccine which gave actually much higher titers than the presently-sold vaccines that are recombinant yeast dry vaccines.

But the initial level of ten milliequivalent was set in some of the earliest trials on vaccine efficacy. In which it was found that people who did respond with relatively low titers, but over ten, were universally protected. Or protected at an extremely high rate.

And these were, as you might remember some of those trials, amongst very high risk individuals, primarily gay men in New York City, and these types of people who had a very high attack rate at that time. But what to do about the titers? Because this is an issue that I call a titer creep.

With all the changes in the vaccines, the

changes in the schedules that we've seen, the changes in the doses, the changes in the formulation. We have seen a gradual decrease in the, in at least some of the titers.

But what I'm quite convinced of now is that the long-term studies that have been coming out over the past few years from Alaska and from Taiwan, have shown that people who, once they seroconvert, remain protected against disease.

Now they may be susceptible to actually being infected, but they universally have gotten subclinical infections. And no one has gotten chronic infections, once they've been vaccinated and seroconverted. So this is primarily what we've been operating on at this point.

With I would say one sort of caveat. And that is those long-term studies were done with vaccines that produced relatively high initial titers on the average. And so we don't really have long-term follow-up studies on newer schedules, newer doses that don't produce quite as high titers.

But it does appear that once people seroconvert, they are protected to the extent that the CDC still doesn't recommend booster doses for individuals who are even high risk individuals whose

titers fall below the magic ten level.

CHAIRMAN DAUM: We thank you. You shed light. Someone had their hand up over here and then Mike Gerber is next. Can they refresh my memory. About four hands went up at once. Dr. Griffin, then Dr. Gerber.

DR. GRIFFIN: Well, I guess I'm not going to shed much light on this, I'm just going to ask another question, I think, probably of Tom and Judy, but, so what bothers me the most is that we have it just seems like the most minimal data on the antigenicity of this vaccine to compare and to use and to make a decision on.

I guess, from the top of my head I think okay you know if it were just three or four hundred people instead of one hundred or fewer, actually, that we actually have the data on, we'd just feel so much more confident that this is really correct and real and that we're making our decisions based on solid evidence. You know one way or the other.

But I guess what I would also, so that it addresses number B so that if you don't think they have enough data, how much data do you need?

I guess I don't have a good feeling if my guesstimate of three or four hundred people in these

groups would be a whole lot better or if we're really talking about you need a thousand or two thousand or whatever to make these data much more confident that what we're deciding is correct. I'd just like some feedback on that.

CHAIRMAN DAUM: Thank you, Dr. Griffin. We have Dr. Gerber, Dr. Britt and soon we're going to start really coming to grips with this question head on.

DR. GERBER: Yes. In thinking about this question of efficacy, one population that I thought of that I haven't seen or heard mentioned are former premature infants.

And I just wonder if there are any data, if infants less than 36 weeks gestation were included in any of these trials and if we have immunogenicity or safety data on that population?

CHAIRMAN DAUM: Sponsor? Dr. Howe?

DR. HOWE: So prior to 1996, we did allow former pre-term infants to be enrolled into the clinical trials and that would include Study 011, which actually started in 1995, but there was a time point in 1996 where we began to exclude pre-term infants from, in terms of eligibility criteria, we mandated that the infants be of at least 36 weeks

gestation.

In the 011 trial, despite the fact that we know we have, we allowed former pre-term infants, we did not collect information about gestational age, when they entered the trial.

So the answer to your question is yes there are former pre-term infants undoubtedly in study 011, but we don't know what percentage of individuals. So we don't have data per se.

Can I just make one comment about the number of subjects or the number of individuals in whom we have immunogenicity data for those three lots. And I just wanted to make sure it was clear that in the 027 --

CHAIRMAN DAUM: To clarify something factually.

DR. HOWE: Yes.

CHAIRMAN DAUM: Okay.

DR. HOWE: Yes. In the 027 Study, which was the study in which the Infanrix HepB-IPV was mixed with Hib, the n per group in that study was 360 and that was for immunogenicity, lot consistency and then a comparison head-to-head to commercial Infanrix.

DR. GRIFFIN: But in that same trial then each of the groups though that you were comparing

is in the order of a hundred.

DR. HOWE: No, no, 360 per group.

DR. GRIFFIN: Is that the 2, 4, and 6 month schedule?

DR. HOWE: The 027 Study was a 2, 4, and 6 month schedule, 360 per group. It was a very large n.

CHAIRMAN DAUM: And where did you find that?

DR. HOWE: It's in Appendix, one of the Appendices to the sponsor's briefing document and it's a table in the FDA's briefing document. And I have it as a slide, but --

CHAIRMAN DAUM: Dr. Ball, can you help us?

DR. HOWE: And then, in terms of the comparison of Infanrix Hepb-IPV mixed with Hib, the data pooled and then compared to again on a head-to-head fashion with commercial Infanrix in that trial, the n would be about 1,000 versus 300. And in that trial non-inferiority to commercial Infanrix was demonstrated for each of the three pertussis antigens.

So it's a very large n and we showed lot consistency as well as non-inferiority to commercial Infanrix in that study.

Additionally Study 048 was also a

relatively large study, I don't have the n's in front of me but it was of a similar magnitude and evaluated lot consistency of the same three lots. We're just having trouble finding that data.

CHAIRMAN DAUM: We should put these designs up if we're going, 027, for example, the specific regimens that are being compared.

DR. BALL: If you look at the briefing document from the FDA, the data from 027 on the various pertussis antigens is found on page twenty.

DR. FLEMING: On page twenty. But let's look at the regimens, the slide that shows the precise formulation of the regimens.

DR. HOWE: So this is the design of Study 027. Here's Infanrix HepB-IPV, the three consistency lots from Study 044 mixed with Hib. The n per group was about 360.

And then we had a control arm, which I didn't discuss during my presentation, but was alluded to by Dr. Ball, where Infanrix, again this is a commercial lot, Engerix B, Hib and Oral Polio. This is a U.S. Study given on a 2, 4, and 6 month schedule.

DR. FLEMING: And you didn't present that first arm because?

DR. HOWE: Well at the time I was only

discussing consistency. And that's why during my presentation I didn't make any mention about the comparison to Infanrix. These are the results though for vaccine-response rates to PT, FHA and pertactin.

For groups two, three and four they received, again this is Infanrix, HepB-IPV, the three lots and 044 mixed with Hib. And then this is the results for commercial Infanrix given separately along with Engerix Oral Polio and Hib vaccine.

And what you can see is that comparable rates, vaccine-response rates, actually very high in all of the groups. And as I said when these three groups were pooled and compared to commercial Infanrix, using the same non-inferiority approach, same criteria, the results were such that the Infanrix HepB-IPV was not inferior to each of the three pertussis antigens with response to, with respect to the vaccine-response rates.

And then the next slide shows the geometric mean antibody titers in groups two, three and four, or Infanrix HepB-IPV mixed with Hib so anti-PT seventy eighty-two, for anti-FHA, approximately 300, anti-pertactin 120, that's in each of three groups, and then you see the comparison to commercial Infanrix right here.

And for each of the three pertussis antigens in the GMTs they were shown to be non-inferior to commercial Infanrix.

CHAIRMAN DAUM: Thank you, Dr. Howe. Dr. Britt and then Dr. Stephens.

DR. BRITT: I just got a brief question for Dr. Feinstone about, he mentioned seroconversion to hepatitis B in the long-term protection studies. What does that equate to with the titer?

DR. FEINSTONE: By seroconversion, we mean titers per milli International units.

DR. BRITT: Thank you.

CHAIRMAN DAUM: I'd like to know if there's burning points that haven't been raised yet. Because I'm, what I'd like to do is now ask each Committee member to speak to this question number one. Dr. Stephens you have such a burning point?

DR. STEPHENS: Well I just wanted to clarify the 027 data that we just heard about. That obviously is a different vaccine. It does contain Hib.

I presume the study was done to reinforce the fact of noninterference in some respects. And I just wanted you to clarify that point.

Because I think it is a valid point that

you've added Hib in this particular instance as another antigen and presumably you didn't see interference in that 027 trial.

DR. HOWE: So the 027 Study was originally designed to assess the consistency of Infanrix HepB-IPV mixed with Hib. And lot consistency for all of the components contained in that product and then comparing it to the individual licensed products.

What I can tell you is that in head-to-head studies, the Infanrix HepB-IPV mixed with Hib as compared to separate injections of Infanrix HepB-IPV that is co-administered with Hib, the vaccine-response rates and GMTs to the pertussis antigens are completely comparable.

And again using sort of a non-inferiority equivalence approach, that those two products behave identically in terms of their response to pertussis.

CHAIRMAN DAUM: You can return to this question if you'd like when we get to question three. But for now I'd like to focus on question one, which is are the available data to support, are the data adequate to support the efficacy of this combination for these antigens?

DR. FLEMING: But this is certainly very relevant to the question one.

CHAIRMAN DAUM: Oh, its relevance.

DR. FLEMING: And ironically you've got three-fold as much data just coming back. You wish we had three-fold as much data, we do have three-fold as much data on a different combination vaccine than we've been asked to consider. And now we're trying to put into context what that different vaccine data in 027 contributes.

DR. GRIFFIN: Contributes, I understand.

DR. FLEMING: Contributes to the combination vaccine we've been asked to consider. It's ironic that the one we're being asked to consider in 015 has one-third the database from another combination that we're not being asked to consider.

CHAIRMAN DAUM: Thank you. Dr. Kohl you're up there. I think you're up there and you're the end member of the Committee today.

I'd like to hear your comments and your vote actually at this point on question one. And if you decide they are, your answer to part a is no, then I think you need to address part b. If that could be the format, I'd be grateful.

DR. KOHL: I've been dreading this moment ever since I realized I was in the Dixie Memorial Chair, Dixie Snider Memorial Chair, but I'll take a

shot at it.

CHAIRMAN DAUM: You don't have any grandchildren.

DR. KOHL: Not yet. It's the same old deal with how comfortable do you feel compared to how much do we need this vaccine. And trying to do that balancing act I was and still am somewhat concerned with the initial data presented on the FHA levels and the HepB GMT levels with the new schedule.

I am somewhat pleased with the data that just came out this minute, tripling a little bit of the immune response, but I think the point that it's different vaccine is important. Most of our problems with different vaccines have caused titers to lower not rise. So if anything I guess if something's unexpected I would have expected it to go South not North.

And I'm going to walk the plank and say given what I think is a real pressing need in this country for combined vaccines I will vote yes on this question.

CHAIRMAN DAUM: Thank you very much Dr. Kohl. And then we won't press you to address question b, which is nice. You get off the hook. Dr. Stephens.

DR. STEPHENS: As one of the evil, non-pediatricians on this Committee, I too am a big advocate of combination vaccines. And, in essence, I'm going to join my colleague to my right and walk the plank with a yes on this issue with certain caveats.

I think we are being asked to make certain assumptions regarding the efficacy of this vaccine. I am encouraged more by the 027 data than I am the 015 data that's been discussed. I am somewhat concerned about the issue of the efficacy of this vaccine and all races and ethnic groups which we really haven't heard a lot of data about.

And I'm concerned with the later discussion that we'll have about both Hib and Hib vaccines and Prevnar. But in essence I do think the data, from what I can read, is probably adequate to support the efficacy of the vaccine.

CHAIRMAN DAUM: Thank you very much. Dr. Faggett, you're up.

DR. FAGGETT: Well, as a pediatrician, I too appreciate the need for this vaccine. But I think Dr. Reynolds made the point that we need more data in terms of pediatric clinical trials and studies in general.

I don't think that the data that we've been presented is adequate to support the efficacy at this time, unless somebody as we go around can convince me otherwise.

CHAIRMAN DAUM: Okay, then Dr. Faggett, I have to ask you to do us a favor and address question b and that is what exactly do you need to be adequate?

DR. FAGGETT: I think we need more numbers. I think maybe 300 should be a threshold. Again, I'm not just that knowledgeable statistically, in terms of statistics of it. But I think we do need more numbers to have more clinical data.

CHAIRMAN DAUM: Thank you. Dr. Griffin?

DR. GRIFFIN: Well, I'm on the fence. I'm not going to be comfortable with my decision either way because I don't think there is, for me there's not an obvious answer to this question.

I would be wildly more comfortable with much more data on this particular vaccine, using this schedule in U.S. children. And I think for right now that is going to carry the day for me and I will have to vote no and that I would like more data.

CHAIRMAN DAUM: Can I press you to be a little bit more specific about what more data you need? Because I think it would be helpful to FDA

folks and sponsors and your colleagues about what it is that you're lacking here in terms of --

DR. GRIFFIN: I guess, and the reason I'm on the fence is that I think with more data it will show that everything is fine. Basically I think that this is probably an excellent vaccine, that it's immunogenicity is fine and that these vagaries of not being totally clear would be cleared up and everyone could be comfortable that we were making the right decision and wouldn't have some long-term consequence of lower immune responses or whatever in this group of children.

I'd like mainly, I guess mainly the 015 Study to bem have groups that were larger I guess my, I would be guessing around three or four hundred. I'm not a statistician so that's just what we might guess that would narrow those confidence intervals to having something I would feel more comfortable with.

CHAIRMAN DAUM: So you, I don't want to put words in your mouth, so let me play it back. You're asking for more U.S. immunogenicity data.

DR. GRIFFIN: U.S. immunogenicity data with this vaccine, head-to-head comparison with giving the components separately and diverse population would be great. I think that's actually in there, but more

numbers.

CHAIRMAN DAUM: Thank you very much. Dr. Diaz.

DR. DIAZ: I too am very, very much on the fence regarding the adequacy of the data to convince me of its efficacy and immunogenicity in young children. And being a pediatrician I do recognize the need for combination vaccines desperately. And yet, again, they must be effective and safe.

I am somewhat reassured to some extent with some of the last minute data that was drawn to our attention regarding the 027 trial and yet I do recognize it was a, not the exact same combination vaccine that we're being asked to talk about today.

I would be more comfortable with more data from U.S. children and in particular more diverse populations, albeit there is some data in one of the studies.

So I feel I'm going to have to abstain, actually, in my response because I'm not convinced either way and I'm uncomfortable to vote either way.

CHAIRMAN DAUM: Okay. You made your reasons for abstaining clear. We thank you. Dr. Goldberg.

DR. GOLDBERG: I'm, in my gut I think this

vaccine is probably fine. But the data is presented from the 015 trial, which I'm, really everything rests here, coupled with the lot-to-lot variation make me want more data as well.

And I guess what I would, I mean I'm troubled because it really, really is, I'm also on the fence, but I would have to vote no right now.

And what I would recommend is a head-to-head, two-arm comparison of the size to be determined to make sure, I wouldn't give you a number now. I think one needs to study the data a little bit to make sure that we can be convinced from the numbers that we get from the new trial.

And also I would try to do it in such a way that you can combine both trials so that you can cut the numbers there but in a sense increase your numbers and do sort of an analysis using, of combining the two studies to get at it.

I don't really think it should be that difficult to do it. But you know that's something I'm not going speak to right now. I think though that given the usage that this vaccine is going to have, we really need more data.

CHAIRMAN DAUM: Dr. Fleming? Dr. Fisher I've bypassed you because I presume you spoke. Dr.

Fleming.

DR. FLEMING: I, my perspective's very similar to Judy's. I am hopeful that with adequate information that there is a very good likelihood that we could be reassured. I'm concerned. We're talking about a vaccine that will be administered to hundreds of thousands, millions of infants. And we have gone through extensive studies.

The Italian and the Swedish trials have been marvelous studies that have established efficacy for, for example the pertussis vaccines and I've been convinced in those studies that the multicomponent vaccines are, there is considerable evidence, are more effective.

I don't have a sense that I can tell you I know what FHA's component is. But I'm very concerned about stepping back in efficacy unless what we are achieving with that step back is of very significant importance.

I'm also, and we're going to get to it shortly, concerned that there might be a price in terms of safety with fever.

And so it seems to me that it's very rational to look to an expectation of having more than, and I consider 015 the core study. To having

more than 100 per arm in that study. So I believe that these data do not establish lack of efficacy.

But they don't provide the level of evidence that I think would be appropriate for the FDA to expect in this setting, and hence would argue that the data don't adequately establish efficacy. How much would we need, which is the second part of the question?

I would specifically argue that that question should be answered with some considerable care as one looks more carefully, if you're going to do another study, at whether we can simplify immune responses into a simple threshold. And there are statistical methods that allow us to get at whether that's valid.

It might be that the proper way to assess immune response there is with the multivariant assessment of ways of assessing these immune responses. My general sense though is that we're probably talking about a study that would be three to four-fold larger if not larger and just as a rule of thumb, four-fold larger halves the confidence interval whipped.

It gives you a precision that's twice as great, which is as we can see from 027, compared to

015, certainly of real relevance here. And that sample size relative to the magnitude of use of this vaccine, to my way of thinking, is a very appropriate expectation by the FDA.

CHAIRMAN DAUM: Thank you Dr. Fleming. Dr. Wharton.

DR. WHARTON: Based on the findings in two of the three pivotal studies 015 and 044, both of which were done with the candidate product on a 2, 4, and 6 schedule in the United States, with 484 children receiving that product in study 044 as well as the supporting study 027, also done in the United States on the 2, 4, 6 schedule, with over a thousand children receiving the vaccine ad mixed with Hib, which I believe is unlikely to improve the immune response of the vaccine, I believe the data is sufficient to support efficacy.

CHAIRMAN DAUM: Thank you very much. Dr. Broome.

DR. BROOME: I agree with Melinda. I think she stated it very well. And I think she's included all of the relevant data which are appropriate to consider.

CHAIRMAN DAUM: Thank you, Dr. Broome. Dr. Britt.

DR. BRITT: I apologize to the other members of the Committee and the audience. I was not here this morning so I didn't hear lots of the lively discussion. I did read the material, I've listened to the discussion this afternoon and I am too a pediatrician and I don't enjoy giving children many injections.

However, the injections I give them now seem to work. And I would like to make sure that the succeeding, the next injections I give them also work. I'm having some trouble under, coming to grips with no-inferiority in some of the discussions that Dr. Fleming has given. And I don't believe that I can see the data yet that says that this is efficacious as what we're giving now.

And in terms of the answer to b, I think I would agree with my colleague across the table, Dr. Griffin, we need more patients and we need a more diverse group of patients. And I think that's something that should be really stressed because this is a pediatric vaccine.

CHAIRMAN DAUM: So I want to make sure I understood you. I'm sorry. You're voting no.

DR. BRITT: I'm voting no.

CHAIRMAN DAUM: Okay. I'm not snubbing

the last three members at the table. But they are non-voting members for the purpose of this discussion. And so there remains my vote and I'm solidly in camp with Drs. Wharton and Broome. I think that with respect to the effectiveness issue, I would definitely like to see more numbers.

I kind of wish the large study hadn't been done in Germany with a different schedule. But I'm looking at the individual components of the vaccine and trying to decide whether I really believe we've seen something that concerns me about efficacy. And I really haven't.

The most important concern is perhaps some compromise in pertussis antibody but I'm not sure I know how to interpret the information that I saw about that. So, I would like to see more ethnic diversity and I would actually like to call on colleagues at the FDA to begin to insist on that.

We all seem to want it. I've heard the Committee members say it over and over again, that even studies performed in the United States, tend to maximize participation of individuals likely to come back and perform in the study protocols. And I'd like to see us begin to move beyond that.

I think the risk of sponsor who undertakes

trials internationally is that you're going to have a scheduling problem. You're going to have an ethnicity problem and we're always going to be a little nervous about importing those things directly into this country. But that's not to say they're not valid, can't be done and can't be looked at. You learn a lot from several thousand children in Germany.

So I'm inclined to think that on the effectiveness issue that I vote yes. And report that the Committee votes five members yes, six members no and one absentia. And all of the people who voted no I must say I wanted more U.S. children entered into trials that focused on immunogenicity with an occasional call for more ethnic diversity.

So question one is done. I'd like to take a fifteen minute break. It's three fifteen, we'll reassemble at three thirty and begin with question two.

(Whereupon, the above-entitled matter went off the record at 3:20 p.m. and went back on the record at 3:38 p.m.)

CHAIRMAN DAUM: We are now ready to go back into session. If people would take their seats and finish their conversations.

I'd like to begin by announcing to the