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PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS

ADVISORY COMMITTEE

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OPEN

OPEN SESSION 5

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Thursday, November 4, 1999

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The meeting took place in Versailles Rooms I and II, Holiday Inn, Bethesda, Maryland, at 2:20 p.m., Harry B. Greenberg, M.D., Chairman, presiding.

PRESENT:

HARRY B. GREENBERG, M.D., Chairman

NANCY CHERRY, Executive Secretary

ALICE S. HUANG, Ph.D., Member

KATHRYN M. EDWARDS, M.D.

MARY K. ESTES, Ph.D., Member

KWANG SIK KIM, M.D., Member

DAVID S. STEPHENS, M.D., Member

DIXIE E. SNIDER, JR., M.D., M.P.H., Member

PRESENT (Continued) :

BARBARA LOE FISHER, Member

PAMELA HARTIGAN, Ph.D., Invited Guest

L. PATRICIA FERRIERI, M.D., Invited Guest

MARTIN MYERS, M.D., Invited Guest

GEORGES PETER, M.D., Invited Guest

JOHN LIVENGOOD, Invited Guest

THERESA FINN, Ph.D., FDA Representative

KAREN FARIZO, M.D., FDA Representative

MARGARET RENNELS, Ph.D., Speaker

KENNETH GUITO, Sponsor Representative

CARLTON K. MESCHIEVITZ, M.D., M.P.H., Sponsor Representative

JAMES E. FROESCHLE, M.D., M.P.H., Sponsor Representative

C-O-N-T-E-N-T-S

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

(2:20 p.m.)

CHAIRMAN GREENBERG: I'd like to invite the FDA members to take their seats at the table.

We're now going to start the fifth open session of today's discussions, and we'll start off. Is Dr. Finn around? Ah, there she is. She's going to do it all, do her slides?

(Laughter.)

CHAIRMAN GREENBERG: Dr. Finn of the FDA is going to give us an introduction.

DR. FINN: Sorry about that. Can everybody hear me?

Today the purpose of the discussion today is to discuss a diphtheria and tetanus toxoid and adsorbed acellular pertussis vaccine. This vaccine is manufactured by Pasteur Merieux Connaught, also known as Connaught Labs, Inc.

And Connaught has submitted a product license application supplement requestinglicensure of their DTaP vaccine, Tripedia, for a fifth successive dose.

And in my introduction today, I hope to provide some relevant background for the discussion phase of this afternoon.

After my presentation we're going to hear from Dr. Margaret Rennels, and after Dr. Rennels, the representatives from the manufacturers will give a presentation, and then FDA will provide a presentation also, and that will be done by Dr. Karen Farizo.

So in my introduction today I will touch briefly on the following topics. First of all, I'd like to give a summary of the current DTP schedule, and I'm going to very briefly mention Tripedia, what it was licensed for, and when it was licensed and what indications.

And then I'll talk about the efficacy, duration of protection, and the safety profile associated with DTaP vaccines in general.

And lastly, I'm going to summarize the safety data associated with a fifth successive dose of another DTaP vaccine, ACEL-IMUNE, which is manufactured by Lederle Labs, and this DTaP vaccine is licensed for five successive doses.

And the very last slide will be a presentation of the questions for discussion later.

So the DTP schedule recommendations are on this slide, and what's recommended is that three doses be given in infancy, generally at two, four, and six months of age.

Following the three dose primary series, there are two booster doses, the first given at between 15 and 18 months of age, although it can be administered at 12 months, and then there is a fifth dose, which is given between four and six years of age or just between entering school, and this dose should be given unless the fourth dose is received after four years of age.

Now, I've included in this slide in parentheses the Td immunization, which is recommended between 11 and 16 years of age, and I've included it because pertussis disease is being increasingly recognized in the adolescent population and has been discussed that perhaps this Td should be amended to include a pertussis immunization as well.

So the recommended childhood immunization schedules are written in a publication from the American Academy of Pediatrics, which is called "The Red Book," and 24 editions of this book have bene published since the first in 1938.

And at this stage I'd like to say that I'm indebted to Hope Hurley at the AAP who copied and forwarded the schedules from these various editions for us.

And what I'd like to point out is that

when you review the schedules, the 1966 edition of "The Red Book" includes a five dose schedule, much as we have today, and prior to 1966, the schedule was more variable. For example, in 1964, there were actually six recommended doses, and in the 1950s it was permissible to give partial doses of DTP.

Since 1966, however, the schedule has remained as a five dose schedule, and of course, we should remember that at that time, the DTP that was given was a whole cell DTP.

There have been some modifications though, for example, the age of the infant immunizations and the age of the fifth dose immunization.

Now, the 1994 edition of "The Red Book" included the use of DTaP vaccines for the fourth and fifth dose. These were actually licensed in 1991 and '92 and were permitted for the fourth and fifth dose, and the 1997 edition includes the schedule which permits the use of DTaP vaccine for all five doses.

Now both recommending bodies -- oops, too fast -- both recommending bodies, the AAP and the ACIP, recommend DTaP vaccines for all doses. Both the AAP and ACIP have very similar statements to the one on this slide which I've taken from "The Red Book," and it states that the DTaP vaccine is preferred for

all doses because of the decreased likelihood of vaccine associated reactions, such as fever and local reactions. The frequency of fever and local reactions including erythema, induration and pain or tenderness followingvaccinationwith acellularpertussis vaccine given as DTaP is significantly less than that following administration of DTP.

In addition to a statement similar to this from the ACIP, and the ACIP has a cautionary statement which recommends that whenever feasible the same brand of DTaP should be used for all doses in the series. Data do not exist regarding the safety, immunogenicity and efficacy of using DTaP vaccines from different manufacturers for successive doses of the primary or booster vaccination series.

so there have been some recent developments in the vaccination, DTP vaccination schedule which I'm going to touch on here.

First of all, there has been concern expressed about increasing local reactogenicity.

Secondly, there havebeenquestions raised about the optimal timing of doses, and of course, if you're going to go into that question, it's very important to consider the duration of pertussis protection, what effect would any timing have on

diphtheria and tetanus titers, and of course, how would any of these discussions affect combination products that are currently in use or in development.

And as I mentioned earlier, due to the increasing recognition of pertussis in the adolescent age group, there is interest in including a pertussis immunization at the adolescent Td immunization.

So Tripedia, which is the subject of this afternoon's discussion, is the DTaP vaccine manufactured by Pasteur Merieux Connaught, U.S. The acellular pertussis components are manufactured by BIKEN in Japan, and then the acellular pertussis components are then shipped to the United States where they are combined with diphtheria and tetanus toxoids manufactured by Connaught.

In 1992, Tripedia was licensed for the fourth and/or fifth dose following wholesale DTP primary series, and in July of 1996, Tripedia was licensed for a primary series, for a fourth dose following a primary series of Tripedia, and for the completion of the five dose series following one or more doses of wholesale DTP.

Tripedia is one of four DTaP vaccines licensed in the United States, and the other three are Infanrix, which is manufactured by SmithKline Beecham

and was licensed in January of '97; Certiva, manufactured by North American Vaccine, Inc., which was licensed in July of '98; and ACEL-IMUNE, which was licensed in December 1996 and is manufactured by Lederle.

Of all of these, only ACEL-IMUNE is licensed for five successive doses in the immunization series.

I'd like to state at this stage all of the vaccines that are licensed in the United States were licensed based on efficacy data, and we should bear in mind that we don't have a laboratory correlate to pertussis protection for acellular vaccines, nor is there a well defined serological correlate for the acellular pertussis vaccines.

And all the vaccines currently licensedin the United States were shown to be efficacious following a three dose primary series. In the case of Tripedia, two studies demonstrated efficacy. The first of these was in Sweden, and this evaluated a vaccine manufactured by BIKEN called J-NIH6, and this is an acellular pertussis only vaccine. There's no diphtheria or tetanus component, and this acellular pertussis component is comparable to the pertussis component of Tripedia.

In this study in Sweden, the first evaluated two doses, the first of which was given between five and 11 months of age. The second dose was given approximately seven weeks later, and this two dose series was efficacious. Vaccine efficacy was estimated to be 81 percent with the 95 percent confidence interval, 61 to 90 percent.

An additional study of Tripedia formulation DTaP was conducted in German. This was a case control study and evaluated three doses of Tripedia given at three, five, and seven months of age, and vaccine efficacy was estimated to be 80 percent with a confidence interval between 59 and 90 percent.

And all the other U.S. licensed vaccines were shown to be efficacious also following three doses.

So what do we know about the duration of pertussis protection? Well, the bottom line is there's very limited data, and what data there is has to be interpreted with some caveats and limitations.

The first of these is the follow-up times vary. Secondly, the case definitions vary. Third, the control groups are unblinded, and lastly, but not insignificantly, is that surveillance in these follow-

up studies was often less aggressive than during the primary efficacy phase of the studies.

So in the next two slides what I've done is summarize some of the available data on duration of pertussis protection following DTaP immunization.

so there is data for Infanrix following a three dose primary series, and this data comes out of the large NIAID sponsored study in Italy. This initial study, the NIAID sponsored study evaluated efficacy of Infanrix until the kids were out to about 24 months of age, and the data showed that the vaccine provided approximately -- was about 84 percent efficacious.

There was a publication in 1998 which evaluated a nine month follow-up in these children, and this publication indicated that vaccine efficacy was approximately 78 percent with a confidence interval between 62 and 87 percent.

And at that stage, at the end of that nine month follow-up the kids were approximately 33 months of age.

An additional publication in 1998 evaluated these same children from the Italian study and showed that at four years of age vaccine efficacy was estimated to be about 84 percent. So these kids

had only received a three dose series of the DTaP.

For Tripedia, I believe that there is ongoing evaluation of protection following a three dose primary series in Germany. However, there is some supportive data which comes from J-NIH6 which is that BIKEN manufactured two component pertussis only vaccine comparable to the P component of Tripedia, and when this was evaluated on a two dose schedule in Sweden, they did do some additional follow-up, and this was published in 1992.

And this paperindicatedthat during three years of follow up after the first study, the vaccine efficacy was approximately 77 percent.

There is some data available for ACEL-IMUNE following a four dose schedule, and this data was actually presented in an abstract at this year's ICAAC, and from the abstract the information indicated that during the five years after a four dose series, the vaccine efficacy was 88 percent with a confidence interval between 76 and 97 percent.

However, the abstract did state that although the number of cases was small and the confidence interval large, there was an apparently decrease in efficacy starting four years after the fourth dose in the DTaP recipients.

So what about the overall safety profile of DTaP vaccines? Well, when given in a primary series, it's clear that the common systemic adverse events occur less frequently than following administration of the whole cell DTP vaccine. Local reactions occur also less frequently than following administration of whole cell DTP, and also the more serious systemic reactions occur less frequently than following administration of whole cell DTP.

The large NIAID multi-center study evaluated 13 different DTaP vaccines for a primary series, 12 DTaP vaccines for a fourth dose, and six DTaP vaccines for a fifth dose, and a few publications have come out on this.

In 1995, Decker, et al., reported that following a primary series there was an increase in frequency and severity of fever, redness, and swelling with successive doses.

Following a fourth dose, a 1997 publication indicated an increase in the frequency of fever, irritability, pain, redness, and swelling relative to dose three.

And the fifth dose publication is actually in press in Pediatrics, I believe will be published early in the year 2000, which shows that there was an

increase in frequency and severity of redness, swelling and pain relative to dose four.

Now, what do we know about severe local reactions following booster doses of acellular pertussis containing vaccines? This, what I'm going to present here, is what's available in the published literature.

In 1987, there was a publication which arose out of a visit to Japan from a group of U.S. scientists to evaluate the Japanese experience with DTaP vaccines, and from this paper or in this paper they noted that the frequency of local reactions increased with successive DTaP doses, particularly after the fourth.

They reported one study which evaluated a booster dose of DTaP vaccine and noted that redness and swelling greater than ten centimeters occurred in approximately four percent of subjects.

The paper did state that extreme reactions, which were defined as swelling of the arm to the elbow or wrist, were rare.

In 1989 Marta Granstrom published a follow-up to a Swedish study, and children who had received two or three doses of AP, acellular pertussis component only vaccine received a booster dose of J-

NIH6, and she noted that in those children, swelling greater than or equal to ten centimeters occurred in 3.1 percent of subjects.

And in the discussion of that papers, she states that whole thigh swelling occurred in a few cases, but we don't exactly know how many.

In 1997, Schmitt, et al., published on a study which evaluated a fourth successive dose of Infanrix, which is the SKB DTaP vaccine, and they noted that entire thigh swelling occurred in approximately 2.5 percent of the children who received that fourth dose.

So as I mentioned earlier, ACEL-IMUNE is a DTaP vaccine manufactured by Lederle Labs, and it is licensed for five successive doses. And in the next few slides, I'd like to provide a brief summary of the safety data and focus on the local reactogenicity data following the fifth successive dose.

So this table was taken directly out of the package insert for ACEL-IMUNE, and it shows the percentage of adverse events, which occur in children who received a fifth successive dose of ACEL-IMUNE. The data from this table was accrued in four separate studies. These studies were performed in the U.S. and in Germany and evaluated a fifth dose of two separate

formulations of ACEL-IMUNE.

The first two studies evaluated a fifth dose of ACEL-IMUNE in which the target aluminum was 0.15 milligrams of aluminum per dose. The last two studies evaluated the currently marketed formulation in which the target aluminum is 0.23 milligrams of aluminum per dose.

You note this last study here is the large multi-center NIAID study.

In the fifth dose studies, the children who received a fifth dose were a subset of those who had received a primary series and fourth dose. Okay? In general, safety monitoring was accomplished by parents how filled out diary cards for three days post vaccination. Local reactions were solicited: redness, lump or hardness, pain and/or tenderness.

And I would like to point out that in one study, the NIAID study, swelling was solicited. To my knowledge, swelling was not solicited in the other three studies.

The actual sizes of local reactions greater than 20 to 24 millimeters was measured, except in one study, which was 69. Arm circumference was not measured.

I'd like to show, first of all, for you to

get a feel for the fifth dose studies; I'd like to show the safety data for the whole series in the next slide in a very summarized form.

So this slide indicates whether the frequency of an adverse event increased in frequency with successive doses. So an arrow here indicates whether the adverse event increased between dose one with successive doses through the five dose series.

So the adverse events were any redness, any induration, tenderness, and significant redness and significant induration, and significant was defined by the manufacturer as redness or induration greater than 20 to 24 millimeters.

For some of these events, the information was not available, NA.

Okay, and I think you can see quite clearly that between dose one and dose five the frequency of adverse events increased. There was one study, 69, where any redness remained the same with each dose at about 26 to 27 percent.

I've pulled out here the largest study, and I've shown here the frequency of the specific event at dose one and dose five. So, for example, for significant redness, which was redness greater than 20 to 24 millimeters, you can see that at dose one, zero

percent of the children reported that level of redness, whereas by dose five 16 percent of children had that level of redness.

Okay. So now if we just focus on the fifth dose reactions, this table shows the percentage of children in each study who reported redness greater than 2.4 centimeters by actual size, and in this column here I've indicated the actual size of the reaction in centimeters, 2.5 to 4.9 centimeters, five to 10.9, 11 to 20.9, and 21 to 25.2 centimeters.

In Study 69, the actual sizes of reactions greater than 20 to 24 centimeters was not solicited. However, there was one child who reported erythema and swelling between the shoulder and the elbow and was visited at home by a study nurse.

In the other studies, redness between 2.5 and 4.9 centimeters occurred in between four and 14 percent of subjects. Redness between five and 10.9 centimeters occurred in between 11 and 23 percent of subjects.

There was one subject in the larger study, Study 69, who reported redness of 25.2 centimeters, and this is the same subject that I've indicated down here.

This subject, the erythema occurred from

shoulder to elbow and was accompanied by swelling, itchiness, and tenderness, and it resolved by seven days post vaccination.

This slide shows the percentage of children in each study who reported induration greater than 2.4 centimeters. This was not measured in Study 69.

Now, you should also note that in this NIAID study the number I've recorded here is actually the percentage of children who reported swelling of this specific size, and you can see that for induration between 2.5 and 4.9 centimeters, between six and seven percent reported this level of induration.

For induration between five and 10.9 centimeters, between four and 20 percent of subjects reported this level of induration. No subject reported induration of the entire arm.

So in summary, therefore, the DTaP is given in a five dose recommended schedule, which is the same as that for the whole cell DTP schedule.

The data on duration of protection following administration of three or four doses of DTaP is limited, and local reactogenicity increases following successive doses of DTaP vaccines.

For ACEL-IMUNE, the frequency and severity of local reactions increases with successive doses. For the ACEL-IMUNE fifth dose data, approximately 11 to 23 percent of subjects reported areas of redness five to 10.9 centimeters. Redness shoulder to elbow was seen in one subject.

Approximately 3.37 to 20 percent of subjects reported induration five to 10.9 centimeters. Induration of the entire upper arm was not reported.

We would just like to state that package inserts for the licensed DTaP vaccines will be reviewed and revised, if necessary, to incorporate more detailed descriptions of severe local reactions with successive doses.

And lastly I'd like to state the questions -- I do realize the first is not a question -- that we would like the committee to discuss today.

First of all, we would like the committee to discuss the safety data submitted to support the licensure of Tripedia for a fifth dose following four previous doses of Tripedia.

And the last question is: what, if any, additional studies should be performed?

And when the committee discussed this, we would like the committee to include -- to consider

some of the information that I presented today in this introduction.

CHAIRMAN GREENBERG: Well, thank you, Dr. Finn.

That went a little over. I will ask the next speakers to try to stick within their time frame, but that was a tremendous amount of data that you summarized for all of us, and I can't believe having to review all of that actually.

We have a little bit of time for some questions, panel members. Do I have any questions?

Ms. Fisher.

MS. FISHER: Was there any attempt to look at whether the children who had these really severe local reactions, whether it correlated with the titers to pertussis toxin and FHA?

DR. FINN: I think you're going to hear some more information on that in the next talk, I believe, from Dr. Rennels, but in these particular studies, to my knowledge, no.

CHAIRMAN GREENBERG: Dr. Peter.

DR. PETER: In the discussion of duration of protection, it occurred to me is the decay of antibody following administration of acellular pertussis the same as with whole cell?

In other words, I realize we don't have a surrogate of protection, immunological surrogate, but I wonder if there are more prolonged antibody titers as a result of the specific concentrations of different antigens.

DR. FINN: What I can tell you is that the decay is very rapid. I think probably Dr. Edwards can probably answer your question better than I can.

Do you have any further things?

DR. EDWARDS: The titers in general with the ACEL start out higher, but they really, as Theresa said, really go down very, very quickly.

CHAIRMAN GREENBERG: I'm not sure I know your name. so --

DR. FINN: Dr. Livengood.

DR. LIVENGOOD: Thank you.

I had a question about the duration of protection not from the antibody, but from the clinical efficacy.

DR. FINN: Yes.

DR. LIVENGOOD: I guess I'm a little confused about continuing to call it vaccine efficacy when you no longer have a control group, and so there is at least in some of these places, there has been descriptions of great decreases in the community of

pertussis, and without an equal opportunity for exposure, I'm a little hesitant to consider those as firm estimates of vaccine efficacy in terms of duration out a little while without a control group or at least some document that the children still have an equal opportunity to be exposed.

DR. FINN: Some of those studies do have control groups, and although what has often happened is that at the end of the main phase of the study, the study is obviously unblinded, and they offer vaccination to the DT group, but there were.

But there were in the Italian study, for example, a group of children who did not take the pertussis, offered pertussis, immunization, and so they have remained as a control group, but you're right. I mean, obviously presumably the burden of disease in the population as a whole will go down, yes.

CHAIRMAN GREENBERG: I have time for one more questions.

Dr. Peter.

DR. PETER: What is the schedules that have been adopted in Europe where the ACEL pertussises have been used in most countries, but not all?

DR. FINN: I don't actually have all of

that information. We do know or we believe that in Germany, for example, which is where a lot of these studies were done that DTaP vaccines are given on a four dose schedule with three before the first birthday, and then a fourth dose sort of about 15 to 18 months of age.

To my knowledge, they do not give a fifth dose.

DR. PETER: We don't know about Sweden. Of course, in Sweden, they're using, I think, the --

DR. FINN: I think in Sweden it's a two, five, 12 schedule.

DR. PETER: Right, but it's a five component vaccine that they've chosen.

DR. FINN: But there are parts of Sweden that are actually only using the single component Certiva vaccine.

CHAIRMAN GREENBERG: Okay. Thank you very much, Dr. Finn.

We'll now move on to Dr. Margaret Rennels, who will tell us some more about this swelling.

DR. RENNELS: Okay. Actually if you could raise the lights to the point where people can still see the slides so that not everybody falls asleep after lunch.

On behalf of my colleagues, I'm going to present some information on extensive swelling after booster doses of several acellular DTP vaccines that were evaluated in the NIH sponsored, multi-center trials. The data I'm going to present to you are going to be published in Pediatrics' electronic pages in January, and the safety and immunicity results of the entire trials have been either published in Pediatrics or are going to be published in Pediatrics also in January.

It was Dr. Mike Pichicero who organized these fourth and fifth dose studies. Dr. Kathy Edwards and Mike Decker organized the primary series studies.

The reason I did this evaluation was because my nurse called me from the practices during the NIH multi-center trial to say, "I've got a kid here who has swelling of the entire thigh," and this happened a few more times, and that got me interested.

So the specific purposes of my evaluation, if you could focus that a little, please, were to determine the rates of severe swelling reactions after doses four and five of the same DTaP vaccine to try to ascertain whether severe reactions occurred with different DTaP vaccines, and to evaluate associated

reactions.

Further, I explored the relationship between the rates of swelling and different antigen contents for the quantity of different antigens, and finally, compared the pre and post dose levels of antibodies to pertussis, diphtheria and tetanus toxin in children with and without entire upper limb swelling.

Subjects, toddlers who had been given a primary series of one of 13 different DTaP vaccines or one of two whole cell DTP vaccines received a fourth dose of the same vaccine. A fifth dose of the same DTaP vaccine was given to children who were still available, meaning those children who had not already gotten their preschool dose, which unfortunately was a minority of the cohort.

Different vaccine was given at dose four or five if the original DTaP was no longer manufactured, as several weren't.

Reaction assessment. Parents were asked to measure in millimeter the greatest diameter of erythema and swelling and record it on a diary card. Entire limb swelling was not anticipated. Therefore, it was not directly solicited. Instead, we reviewed the comment section of each reaction form after each

booster dose and looked specifically for spontaneous reports of entire limb swelling. This probably underestimated the true rate.

Serology. Blood was obtained just before and one month after vaccinations, and the antibody to pertussis toxin was measured in the labs of Bruce Meade, Kathy Edwards, Mike Pichichero, and then the tetanus and diphtheria antitoxin levels were assayed by Jenny Losonsky at the Center for Vaccine Development.

Subjects. The number of subjects who received the same DTaP for the fourth dose as they got in the primary series, there were 1,015 children. Seventy-four got mixed DTaP schedule. Sixteen received a whole cell DTP for all four doses, and then 246 received whole cell DTP boosted by a DTaP.

A fifth dose, 122 children received the same DTaP for all five doses. One hundred forty-six received a mixed DTaP schedule, and only four children received the same whole cell for all five doses.

The rates of entire upper limb swelling are shown here. After dose four, the toddler dose, 20, or two percent of the children given the same DTaP, the parents reported entire thigh swelling. One of the 16 children who had gotten the whole cell DTP

for four doses had entire thigh swelling reported.

Interestingly, none of the children who got a primary series of whole cell DTP and then were boosted by DTaP was entire thigh swelling reported, and in fact, the difference between these two is statistically significant.

Now, after dose five, none of the 121 children who got the same DTaP were reported to have entire upper arm swelling. I think that's an artifact of small numbers though because, indeed, four of 146 who got mixed DTaPs, or 2.7 percent, did report entire upper arm swelling.

Parents reported that this entire thigh swelling after post dose four began primarily on days or was noted primarily on days one and two, with a few on day three.

There was no difference in the rates of fever in children who had the entire thigh swelling versus those who didn't. However, irritability, pain, and erythema were more common in the children who had entire thigh swelling. Actually more properly put, it was more commonly reported. It may have been just more commonly notedbecause the parents were impressed with the thigh swelling.

This, I think, is important and

interesting. Forty percent of the children with entire thigh swelling were judged to be in no pain whatsoever, and I found that rather remarkable. Those who were thought to have pain, it was mainly very mild. Two children were judged to have moderate pain, and three children out of 1,015, or 15 percent of those with entire thigh swelling, were thought to be in severe pain, which was defined as cried when the leg was moved.

Duration is self-limiting. There were no necrotic reactions, no ulcerative lesions. I think perhaps the most important finding of this evaluation was that entire thigh swelling was reported after dose four with nine of the 12 different DTaP vaccines evaluated. So this is not an isolated phenomenon, and that the involved DTaP vaccines contained between one and five pertussis antigens. So even monovalent PT vaccine combined with diphtheria, tetanus, and aluminum can induce these reactions.

And the rates of entire thigh swelling after dose four by vaccine are listed here. The numbers in parentheses are the number of pertussis components. The U.S. licensed vaccines that were in this trial are in white.

One might get the impression that there

may be some variation in the rates, but these numbers are so tiny that I wouldn't put much stock in that.

Now, here is a linear regression showing here the percent of children experiencing entire thigh swelling post dose four plotted by quantity of diphtheria toxoid in the vaccine. Each dot represents one vaccine.

You can see that, indeed, this linear regression line indicates a significant association between the swelling rate, increasing swelling rates with increasing diphtheria content, but it didn't hold for every vaccine. You can see there are exceptions.

Here you probably can't see them very well. Here are more linear regressions. Here's for pertussis toxoid content, tetanus toxoid content, and this is aluminum content. None of these associations were significant, but I think you can get maybe an idea that there's perhaps a trend for increasing rates of swelling with increasing quantities of the vaccine antigens and aluminum.

We did not observe anycorrelationbetween the rates of entire thigh swelling and pre or post vaccination serum levels of antibody to pertussis toxin, tetanus toxin, or diphtheria toxin. Both the distribution between the cases of entire thigh

swelling and controls were the same, and the geometric main concentrations of antibody were the same.

Now, recall there were no children who would get five doses of the same DTaP who had entire upper arm swelling. So with this group I looked at swelling greater than 50 millimeters after dose five, and the rates of swelling greater than 50 millimeters are shown here, and again, if you post hoc read the data and don't correct for multiple comparisons and ignore tiny numbers, you get an idea there may be differences in rate, but I don't think that's fair with these little numbers.

The relationship between the rates of these lesser degrees of swelling and vaccine contents did not show a significant association with diphtheria. Instead post dose four entire thigh or greater than 50 millimeters of swelling correlated with pertussis-toxoid content and after dose five it correlated with aluminum content.

So in summary, severe swelling reactions were seen post booster doses of many DTaP vaccines. They are associated with other local reactions, but the sever pain was uncommon, only three children of the 1,015, and they're self-limited.

The etiology of these severe swelling

reactions probably is multifactorial, although entire thigh swelling was associated with DT. Lesser degrees of swelling were not and instead correlated with pertussis and aluminum, but at different doses.

Finally, I think part of the problem in trying to figure out the meaning of all this is anticipated and consistent data was not collected and reported. I think in future studies, particularly in DTaP combinations where we have a chance to do it differently, I think we should assess the association of swelling reactions with pain.

And I say that because parents of children who didn't seem to have any pain were really remarkably unconcerned about these reactions. I think it's the severe swelling with serious pain that we need to be worried about.

We reallyneed standardized collection and reporting of data. For example, it would be very useful if consistently the thigh or the deltoid was injected in these studies. If we're going to get circumference, limb circumferences, where? If it's going to be in the thigh, it makes sense to have it at the injection site. If it's in the deltoid, that's a little difficult, and perhaps it should be mid-humerus.

And finally, if we do collect circumference measurements, it would be very useful to have consistent definitions of mild, moderate, and severe swelling or perhaps, as we do now with some antibody displays, perhaps we should take the circumference and display them as reverse cumulative distribution curves with rates of swelling.

Those are my comments.

CHAIRMAN GREENBERG: Thank you very much, Dr. Rennels.

We have some time for a few questions. Ms. Fisher.

MS. FISHER: Anecdotal evidence that we have collected suggests that children who have a severe local reaction on an early dose, doses one, two, or three, go on to have a more severe systemic reaction on a subsequent dose. Was that your experience or did you look for that?

DR. RENNELS: Well, it wasn't consistent. I can tell you that of the four children at my site, University of Maryland, who had entire thigh swelling, all of them had -- well, we were able to track down three of them at age five, and all three had received a DTaP vaccine, maybe not the one they had received for the primary series, and none of them had excessive

reactions that the parents could remember, and I think they would remember a severe reaction, but that's all I can tell you.

CHAIRMAN GREENBERG: No other questions? Okay. Thank you very much, Peggy.

We now move on to the sponsor's talk, and I think we have Dr. Kenneth Guito and Dr. Carlton Meschievitz from PMC.

MR. GUITO: Good afternoon. I'm Ken Guito, Director of Regulatory Affairs at PMC.

I'd like to thank our CBER colleagues for the invitation here today. We're happy to be here to present to the VRBPAC.

We'd like to thank Drs. Rennels and Finn for their lead-in presentations. It's a nice segue to our presentation.

As you know, we're here today to talk about the fifth consecutive dose of the Tripedia vaccine in children four to six years of age, and we think as you'll see it's quite an acceptable safety profile in this group.

As a little historic reference, each dose of Tripedia vaccine contains acellular pertussis concentrate, diphtheria and tetanus toxoids. The acellular concentrate contains equal quantities of

lymphocytosis promoting factor, or pertussis toxin, and filamentous hemagglutinin.

With regard to the toxoids, 6.7 Lf of diphtheria and five Lf of tetanus. Those toxoids are the same toxoids that have been used in our whole cell DTP vaccine for over 40 years, and that level of diphtheria is the lowest level of any currently licensed acellular vaccine.

The vaccine also contains thimerosal currently, and we're currently working with our CBER colleagues toward the introduction of a thimerosal-free presentation.

Dr. Finn gave us the history of the license approvals, but I'll run through it again. In 1992 Tripedia was licensed for the booster dose at 15, 18 months, and four to six years of age following a primary series of whole cell DTP.

In 1996, we presented to the VRBPAC an infant indication for two, four, and six months of age, and that vaccine was subsequently licensed by CBER also in the same year and allowed pediatricians to immunize children at two, four, six, and 15 to 18 months of age. It also represented the first infant approval in the U.S.

Also at that time we presented a limited

amount of data in children who had received five sequential doses of vaccine up to their sixth birthday.

Since the Tripedia infant approval in 1996, approximately 29 million doses have been distributed and a total of 41 million doses have been distributed prior to -- including the years prior to 1996.

From August of '96 through September of '99, approximately 43 percent of all the DTaP doses distributed through the vaccine for children program were Tripedia, and although the numbers are a little hard to pin down, we believe the same percentages are accurate for the private sector.

Therefore, there's a cohort eligible for the vaccine coming due probably in early Q2 2000.

As I mentioned, when we presented data in 1996, we had a limited amount of data in children who have received five sequential doses of the vaccine. We wanted to better characterize their responses in a safety profile in that population. Therefore, we initiated two trials.

And Dr. Carlton Meschievitz is here to talk to you about those today. One is a continuation of our German efficacy trial. The other is a trial in

U.S. infants.

After that presentation, we'll be happy to take any questions you may have.

DR. MESCHIEVITZ: Good. Thank you and good afternoon. My name is Carlton Meschievitz, and with me today are colleagues from Pasteur Merieux Connaught. In addition to Mr. Guito, James Froeschle was the study monitor for the German trial, efficacy trial, and the booster trials, including the data you'll see today. For the U.S. trial, I have Dr. Loretta Wubbel, who was the monitor for that trial, and we have Dr. Thomas Zink from Germany who was involved on site monitoring of the recent data.

I'd like to, before I present the results of the trials, go over the safety data with Tripedia that existed at the time of licensure in 1996, and at that time, we had data on the primary series, the fourth dose booster, but a very limited amount, only the 18 children that were presented earlier by Dr. Rennels relative to the fifth dose.

However, from that data, it appeared to us that there was no suggestion of any increase in systemic reactions. However, compared with the first four doses where reaction rates were actually fairly similar among the doses, we did see a suggestion of a

larger number of reports of erythema and swelling.

First, the German trial. As mentioned, this trial was a continuation of the efficacy trial that was conducted in Bavaria. The study cohort, to try to keep it similar to the data that has been collected by the NIH, we attempted to collect adverse events in the same population through sequential doses, and so we had extensive adverse event data in children who had received vaccine at three, five, seven, 15 to 24 months of age, and four to six years.

This is an open labeled, descriptive study and was conducted between March of 1998 and September of 1998.

When the trial began, the original case report form diaries contained careful information on common local and systemic reactions that occurred during the first three days following immunization, and then a follow-up visit about a month later to determine other adverse events that occurred post immunization.

Also, at that time reactions were classified as less than two and a half centimeters, between two and a half and five centimeters, and greater than five centimeters.

About midway through the trial, the last

241 children immunized had a more detailed and careful evaluation of the common local and systemic reactions up through 14 days, and so this included more information on duration and also on actual size.

At this point we began doing precise measurements of all reactions that were larger than five centimeters to see exactly how large they did become.

We also drew sera in a subsequent of the children in this trial, and that data has only been preliminarily analyzed and will be further analyzed and presented to the FDA.

Also, all adverse events were followed until resolution.

so looking at the first three days following vaccination where we had a study cohort of 580 children, you'll note that redness, swelling, and pain occurred in approximately 60 percent of study participants.

For a redness, 11 percent of subjects had redness less than 2.5 centimeters, 17 percent between two and a half and five, and 31 percent greater than five centimeters.

For swelling, the breakdown was 18 percent, less than 2.5; 18 percent, greater than 2.5

but less than five; and 25 percent greater than five centimeters.

For pain, the majority of the pain, in fact, pain associated with vaccination in 38 percent of individuals was mild in nature, and that was defined as slight reaction when the injection site was touched, and 18 percent moderate and two percent classified as severe pain.

It would be important to note that none of the local reactions occurred or the initial reaction all occurred within the three day period.

To better characterize the larger reactions, you will see here that we have labeled to classify them between five and 11 centimeters. Redness occurred in 25 percent of those subjects, 17 percent for swelling. Between 11 and 16 centimeters, three percent for redness, two percent for swelling. And then greater than 16 centimeters up to 25 centimeters, you can see less than one percent.

However, complete upper arm swelling, which was defined as swelling from the elbow to the shoulder, occurred in two of the individuals for redness and 2.4 percent for swelling. I'll describe these reactions in a little more detail a few slides from now.

Looking at the time course of the reactions, you'll see on the Y axis the percentage of subjects reporting, and on the X axis the days post immunization with day zero being the day the immunization was given.

And you'll notice on the day of immunization, the most common report of local reaction was pain, followed by swelling in the red, and redness on the white bar.

You'll also note that the reactions all tended to peak within the first three days, began tapering off by day three, four or five, and the majority were gone by the end of the first week, and nearly all of the reactions had disappeared by the end of the second week.

Looking at systemic reactions, temperature, oral temperature greater than 38 degrees Centigrade was seen in 3.8 percent of subjects. Fussiness occurred in 19 percent of subjects, but, again, the largest percentage of fussiness occurred as mild, meaning periodically more irritable than usual, but with normal activity. About six percent had either moderate or severe fussiness. Drowsiness, 15 percent; anorexia and vomiting, all less than ten percent.

Now, a description of the large local reactions, and these are all of the reactions that occurred during the trial that extended essentially from the elbow to the shoulder, are shown here. All 14 of them had swelling present.

Perhaps we could focus the slide a little bit. I see that the headings aren't crystal clear.

Ten of the swellings were associated with redness, but not all of them, and again, similar, I think, to Dr. Rennels' data, there was very little pain. In fact, there were five reports of pain, all of which were reported as mild.

Only two of the parents brought their children in to see a physician because of questions about the reaction, and you'll notice here the duration of redness in days. The resolution of the complete upper arm swelling occurred within one or two days, and the complete resolution of the redness when the entire redness was gone from the arm occurred between two and five days post immunization.

For swelling, the complete upper arm swelling disappeared between one and three days post immunization, and the entire resolution of all swelling was gone between three and six days following immunization.

And I also would like to note here that there were no -- none of these individuals had a fever greater than 38 degrees centigrade.

Now I'll switch to the U.S. database. This is data on the fifth consecutive dose of Tripedia or a Tripedia containing combination. Actually the fifth dose of Tripedia in children who had received Tripedia or Tripedia containing combination for the four prior doses.

And this is an analysis of the first 96 subjects enrolled in the trial, and again, as you can see here, very similar to what we found in Germany. Approximately 60 percent of individuals had either erythema, had swelling or tenderness, and 54 percent pain.

The breakdown here in the U.S. was 22 percent of children with erythema less than or equal to an inch; 18 percent, one to two inches; 21 percent, greater than two inches, and I'll go into more detail on those reactions later.

Swelling, 30 percent equal to or less than an inch; 20 percent, one to two inches; 13 and a half percent, greater than two inches.

Tenderness, themajority, 48 percent, were considered mild, which was the symptom present, but

usual daily activity was not affected, and there were no instances of severe tenderness.

Similarly for pain, 45, 46 percent were considered mild, eight percent moderate, and none severe, and you'll notice the date of onset of all of these symptoms was primarily in the first three days, and for erythema and swelling, was entirely within the first three days.

Description of the reactions greater than two inches is seen here. Reactions that were between two and four inches occurred in 11.5 percent for erythema, seven percent for swelling. Reactions four to six inches occurred in eight percent for erythema, five percent for swelling, and there was only one reaction larger than six inches, and that was one child who had an eight inch reaction. So the total rate of these reactions were 20 percent for erythema, 13.5 percent for swelling greater than two inches.

Here you'll notice a typo. When we got the slides made up, that is not a question mark. That should be equal to or greater than, and this funny little symbol is supposed to be a degree sign, but our computer had a glitch.

You'll notice here for systemic reactions two of the individuals had temperature between 38 and

39 degrees, none greater than 39 degrees.

Irritability occurred in the U.S. at a rate of 33 percent, with 28 percent being mild in nature, five percent moderate, and none severe.

Drowsiness, 16 percent.

Anorexia, 13.

And vomiting, three percent.

Finally, for both trials, that is, combining the 580 children in Germany and the 95 in the U.S., there were no serious related adverse events. In fact, there were only two hospitalizations, both in Germany and both considered by the investigator to be unrelated to vaccination. One was adenoiditis, and the other one was an appendicitis.

We also had four vasovagal fainting type episodes. All occurred in children who also had blood draws at the time of vaccination, and we had one instance of a supervision cellulitis that responded to antibiotics, and so all reactions resolved quickly.

So going back to the table I began my talk with, I'd like to end it now completing the picture with the larger numbers of children shown here in the fifth dose boxes of this overhead.

Again, you'll note that for systemic

reactions, the reaction rates are more or less comparable to those seen in the first four doses of the vaccine. However, the local reaction rates, particularly erythema and swelling, occur at a higher frequency than seen with the first four doses and a remarkably similar rate between German and U.S. children.

I'd like to just show one slide reminding people of the previous standard of care, which was whole cell DTP, and this is information from two publications, one by Bernstein in the American Journal of Diseases of Children, evaluating five doses of the Connaught whole cell DTP, and an often quoted paper by Cody and colleagues published in Pediatrics in 1981, and I'll particularly draw your attention to fever, which occurred at a rate of 18 percent in the Bernstein manuscript with the one whole cell DTP, and Dr. Cody who used -- actually assessed vaccine by three manufacturers, Parke Davis, Lederle, and Connaught, found fever greater than or equal to 38 degrees in about 46 percent of individuals. So we're seeing much lower rates of fever at the fifth dose.

In addition to the information or as a supplement to what Dr. Rennels presented, part of the trial that she, Dr. Pichichero and others participated

in did look at the fifth dose, and as Dr. Reynolds mentioned, unfortunately the numbers are small. However, it is the only comparative trial that I'm aware of looking at different vaccines in the same population by the same investigators evaluated using the same criteria, and you'll notice here Tripedia, ACEL-IMUNE, which is the only product currently licensed for the fifth dose among the acellular products, and whole cell vaccine.

Given the very limited or the very limitations of the small numbers, nonetheless I think it's clear that Tripedia compares favorably with the other acellular products.

So in summary, following the fifth dose of Tripedia compared to reactions following doses of two, four, six, and 15 to 24 months of age, we do find an increase in local reactogenicity, but no increase in systemic reactogenicity.

The local reactogenicity for Tripedia was similar and for fever was dramatically reduced when compared to historic controls receiving a fifth consecutive dose of whole cell DTP, and Tripedia is well tolerated, and common, local and systemic events resolve spontaneously without sequelae.

And again, for the first four doses now,

we have distributed around 41 million doses of vaccine.

So I'm finished with my presentation, and I'm open for any questions that might be on anybody's mind.

CHAIRMAN GREENBERG: Thank you very much.

Panelists, do you have, committee members, any questions here?

It's remarkable to me. Everybody seems to have the same data. That's always a good sign.

Dr. Estes.

DR. ESTES: For the subset of children that were studied in Germany, were those children -- how were they chosen or found for the fifth dose?

DR. MESCHIEVITZ: I'll let Dr. Froeschle answer that question. He was the study monitor for that trial.

DR. FROESCHLE: There were 63 original investigators in the trial, and we asked the other investigators who would want to volunteer for this trial. So it's a matter of just a volunteering to be part of the trial.

And then they just took all comers. There's no randomization. We just whoever we could get for that trial.

CHAIRMAN GREENBERG: Other questions?

If not, we will jump ahead of our schedule and move on to safety of the fifth dose by Dr. Karen Farizo.

DR. FARIZO: Good afternoon. My name is Karen Farizo. I am the clinical reviewer from FDA for the product license supplement for approval of a fifth successive dose of Tripedia.

Much of the information that I intended to present as background has already been presented. So I will go through the first several slides very quickly, and then we'll review the safety of Tripedia for the first four doses to provide a frame of reference for review of the fifth dose data, and then towards the end of the presentation, I will present some safety data on the fifth successive dose of whole cell pertussis vaccines, and that will be historical data.

You're already heard about the formulation of Tripedia. There are two pertussis antigens, diphtheria and tetanus toxoids adsorbed onto aluminum. You've already heard that the vaccination schedule in the U.S. is for five doses, including two boosters, and the one at four to six years of age is the one that is under consideration today.

You've heard from both Dr. Finn and the sponsor about the licensed indications of Tripedia. The requested indication is a fifth dose following four previous doses of Tripedia, and as you've heard from the sponsor, in the second quarter of 2000, the initial cohort of children who received a primary series according to the recommended schedule will be eligible for the fifth successive dose.

And before presenting the data on the fifth dose, I would like to just give an overview of the safety profile of the first four doses.

Serious systemic adverse events following Tripedia were less frequent than that expected of whole cell DTP vaccines. Less serious, more common systemic adverse events and local reactions also occurred less frequently following a primary series of Tripedia than whole cell DTP.

Available data suggest that some local reactions tended to occur more frequently following the fourth dose of Tripedia compared with the third dose.

And in the next few slides, I would like to present some data on local reactions following the first four doses of Tripedia. These data are from a U.S. study in which approximately 500 infants received

a primary series with Tripedia.

You can see that tenderness was reported in between roughly six and 12 percent of infants. Any erythema was reported in between nine and roughly 17 percent. Any swelling in roughly between four and six percent.

You can also see that erythema greater than one inch and swelling greater than one inch were relatively infrequently reported following the doses of the primary series, in less than two percent of subjects generally.

Now, the next two slides will show available data on local reactions following a fourth dose of Tripedia from two different studies. This study was an open label U.S. study, and of approximately 100 children who received a fourth dose, pain was reported in 19 percent within 72 hours following the dose. Erythema and swelling greater than or equal to one inch were each reported in approximately 30 percent within 72 hours following the fourth dose.

These are data from a safety study in Germany. The subjects included here are 738 children who are a subset of subjects who participated in the vaccine efficacy study, and reactions listed here are

those that occurred on the day following vaccination with the fourth dose. Pain was reported in 14 percent; any erythema in 37 percent; any swelling in 20 percent; and erythema greater than an inch in 12 and a half percent.

You have already seen these data from the sponsor. These are from the U.S. NIAID study which evaluated the safety of several different DTaP vaccines, and as you've heard, 135 children received a primary series with Tripedia; 82 received a fourth dose; and 18 received a fifth dose.

These are the only data that we have available at CBER in which reaction rates are available for all five doses from the same study, and that's why I wanted to go through this. You can see that although the numbers of children who received the booster doses, particularly the fifth dose is relatively small, there is a trend apparent of increasing local reactions with the booster doses.

And if we can just for the sake of time focus on the swelling data, you can see that swelling was reported in roughly eight to 11 percent following doses of the primary series; 16 percent after the fourth dose; and 27.8 percent after the fifth dose.

Swelling greater than 20 millimeters was

infrequent following the primary series. I do not have that data point for the fourth dose, but 3.8 percent of children who received a fourth dose reported swelling of a larger degree, greater than 50 millimeters, and 17 percent who received the fifth successive dose reported swelling greater than 20 millimeters.

Now let's move on to the newly available safety data on a fifth consecutive dose of Tripedia and in considering Tripedia for this indication, our primary consideration at CBER is vaccine safety, and because of the increased local reactogenicity with the fifth dose, my presentation will focus on the local reactions.

As you've heard, two studies were conducted, one in Germany and one in the U.S. Both were open label studies with one study group, and the primary objective was to evaluate safety.

In the German study, the population consisted of healthy children four to six years of age, previously vaccinated with four doses of Tripedia. These subjects in the fifth dose study, 580 subjects, had participated in one of two previous studies, a case control study of vaccine efficacy in which over 12,000 infants received Tripedia, or a

smaller immunogenicity study.

To my knowledge, the fifth dose of DTaP vaccines is not routinely recommended in Germany. Recruitment was by telephone calls and letters to parents of eligible children.

The number of children eligible for this fifth dose study was not provided, and if the 580 who participated in this study represent a small subset of those who were eligible, then the results potentially could be influenced by selection biases of unknown direction and magnitude.

And one concern at least theoretically is the possibility that children who had local reactions after previous doses were less likely to participate in the fifth dose study than those who did not, and if these individuals have an increased risk for severe local reactions after the fifth dose, then there is the potential for underestimating both the occurrence as well as the severity of local reactions.

Children receivedone dose of Tripedia and were monitored for safety, and as you've heard, safety was monitored through the use of diary cards. Local erythema and swelling were both solicited and categorized as less then two and a half, two and a half to five, or greater than five centimeters.

There was a protocol amendment after the study was initiated, and as part of that protocol amendment, sizes of local reactions greater than five centimeters were actually measured and recorded, and this required the development of a new diary form. The new diary form was available for 241 subjects, and information on sizes of local reactions greater than five centimeters also was collected for an additional 242 subjects who used the original diary form, but were instructed by the investigator to record this information.

Justverybriefly, roughly four percent of children who received the fifth dose had fever. Fussiness was reported in roughly 20 percent, and drowsiness in 15 percent.

And getting on to the local reactions, as you've already heard from the sponsor, any pain or tenderness, any redness, and any swelling were each reported in roughly 60 percent of subjects. This included two percent of subjects who had severe pain or tenderness, defined as crying when the arm was moved.

Redness greater than five centimeters was reported in 31 percent, and swelling greater than five centimeters in 25 percent.

Now, this slide shows the frequency of local reactions larger than five centimeters according to the diameter measured by the parents. The analysis that you have seen from the sponsor was limited to the 240 or so children who had the new diary forms which actually solicited this information.

The data that were submitted to the supplement at CBER included 490 children, those who had the new diary forms and those who did not. I would just like to say that the data that you've seen from the sponsor in these data are generally consistent, and you can see that of reactions greater than five centimeters, most of them were less than 11 centimeters.

However, three and a half percent of children had redness between 11 and 15.9 centimeters, and 2.9 percent had swelling in this range. A few children had redness and swelling between 16 and 25 centimeters.

In addition, complete upper arm swelling, which was not specifically solicited on either diary form, complete upper arm swelling was reported in 2.9 percent and complete upper arm redness in two percent.

It was not indicated whether children who reported complete upper arm reactions are also

included in these rows. It also seems feasible that children who had reactions greater than 11 centimeters, particularlygreaterthan16 centimeters, may also have had involvement of the complete upper arm, given that these are four to six year old children.

However, the overlap between those with complete upper arm reactions and the children listed here was not clear.

The sponsor also provided an analysis of other reactions that occurred in subjects who had redness and swelling greater than five centimeters, and in the next slide I'll show some of the results for swelling.

And because of the small numbers in these three groups between 11 and 25 centimeters, I have basically grouped or lumped these.

This analysis examined the occurrence of other reactions reported on the day of maximum swelling, and you can see that the majority of subjects who had swelling between five and 25 centimeters also reported pain. Although not shown on this slide, for most of these subjects who reported pain, the intensity was mild or moderate. In approximately nine percent of these subjects the pain

was considered severe, which was defined as crying when the arm was moved.

Of subjects who reported complete upper arm swelling, the frequency of pain on the day of maximum swelling was 35.7 percent. You may recall that of the entire study population, approximately 60 percent reported any pain within three days after vaccination. So the apparently lower frequency of pain in the complete upper arm swelling group compared with these children or the entire study population overall may be due to the small number of subjects or other unexplained factors.

You can see that fussiness was reported in roughly 14 to 28 percent of children with relatively large areas of swelling, not very different from the frequency reported in the overall study population of 20 percent. None of the children with complete upper arm swelling had fever, and four to 11 percent of those with swelling between five and 25 centimeters had fever, and that is similar to the four percent reported overall.

Twenty-eight subjects, or 4.8 percent of the entire study population had redness and/or swelling that led to a medical visit. These are not necessarily the same children that you saw in the

previous slide with extensive areas of redness or dwelling or those with complete upper arm swelling. I don't have that data available.

The local reactions were judged by the pediatricians as mild in approximately two thirds; moderate or interfered with usual activity in approximately one third; and severe, incapacitating in one subject. All were reported to resolve without sequelae.

You've already heard about the U.S. study population. These were healthy children who previously received four doses of Tripedia or Tripedia used to reconstitute ActHIB. They are a subset of subjects who participated in one of two previous protocols. Recruitment was by phone calls and letters, the number of eligible children was not provided. The planned enrollment was 400 subjects. At the time of submission of the supplement to CBER, the study was ongoing and safety data available on 96.

Safety monitoring was similar to that described for the German study, and sizes of local reactions greater than two inches were recorded for all subjects.

The profile of systemic symptoms within three days after vaccination was generally similar to

what you saw for the German study, and for local reactions, as well, data are consistent with the German study, approximately 50 to 60 percent reporting pain, redness or in this case swelling/hardness was solicited on the diary forms.

Redness greater than two inches was reported in 21 percent, and swelling or hardness greater than two inches in 13 and a half percent.

This you've already seen. This is the frequency of local reactions, two inches or larger. Roughly11 percent had redness, seven percent swelling between two and 3.9 inches, and eight and five percent, respectively, had these reactions that were measured as four to 5.9 inches, and one subject had a reaction of eight inches.

There were no reports of entire arm swelling, although that was not specifically solicited.

And now I would just like to show this one slide. You've already seen these data from the sponsor. These are data on whole cell pertussis vaccines.

Overall when considering systemic and local reactions over the complete five dose series, Tripedia and acellular pertussis vaccines in general

clearly have a superior safety profile over whole cell pertussis vaccines.

However, a question that often comes up is how does the observed reactogenicity of acellular pertussis vaccine boosters compare with whole cell pertussis vaccine, and I wanted to address this question because I think it helps provide practitioners and the public health community a frame of reference for what to expect from booster doses of acellular pertussis vaccines, and we need to rely on historical whole cell data to address this question.

This slide shows the frequency of reactions within 48 hours following a fifth dose, a fifth consecutive dose of U.S. licensed whole cell pertussis vaccines in the often cited study by Cody and colleagues, which was published in 1981, and this is the largest study examining safety of whole cell pertussis vaccines of 876 children.

You can see that roughly 45 percent reported redness or swelling, and 74 percent pain. Fever was reported in 46 percent. Drowsiness and fretfulness in 21 and 33 percent, respectively.

And a comparison of this data to those that you have seen on Tripedia suggest a similar frequency of common local reactions following a fifth

dose of Tripedia in whole cell vaccines, and a lower frequency of systemic reactions, particularly fever, with Tripedia.

And anotherquestionthat frequently comes up has to do with whether extensive swelling of the injected limb was a problem with booster doses of whole cell pertussis vaccines, and you have heard from Dr. Reynolds that swelling of the entire thigh was reported in one of 16 subjects who received a fourth consecutive dose of a U.S. licensed whole cell pertussis vaccine in the NIAID study, but what about our general experience with whole cell pertussis vaccines?

Extensive local reactions with whole cell vaccines were recognized as a problem with the whole cell pertussis vaccine widely used in Canada. That is a different vaccine than those that have been licensed in the United States.

Based on a review of the literature, as well as speaking with several clinicians, it seems that extensive local reactions apparently were not recognized and reported as a major problem with whole cell pertussis vaccines in the United States, and extensive reactions were not specifically addressed in the study by Cody and colleagues.

In one of the studies by the Canadian investigators, they state that among the 800 or so children who received a fifth successive dose of the U.S. whole cell pertussis vaccines in the Cody study, that large local reactions, greater than five centimeters in diameter, were infrequent, occurring in less than five percent. This was based on a personal communication that the Canadian investigators had with one of the co-authors of the Cody study.

So to summarize, for common systemic reactions, the overall safety profile of a fifth successive dose of Tripedia is superior to that observed historically with a fifth dose of whole cell pertussis vaccines.

The frequency with which subjects reported solicitedlocalreactions following a fifth successive dose of Tripedia is generally similar to that observed historically with a fifth dose of whole cell pertussis vaccines.

And the frequency of local reactions following a fifth successive dose of Tripedia is greater than that observed with the first four doses of Tripedia in other studies.

Approximately four to nine percent of subjects reported large areas of redness, defined here

as greater than 11 centimeters or greater than or equal to four inches, depending on which study, and approximately four to six percent of subjects reported large areas of swelling. In some cases the redness and swelling involved the complete upper arm. In one study, approximately five percent of subjects had a medical visit for a local reaction. Extensive local reactions resolved without sequelae.

And I think you have heard this afternoon that extensive local reactions have been observed with several different DTaP vaccines when given as a fifth successive dose. In general these reactions appear to be clinically relevant, at least in terms of some discomfort to the subjects for several days.

However, they resolved without sequelae. The pathophysiologic mechanisms of these reactions are not known. We're not able to distinguish between the different types of hypersensitivity reactions based on the clinical data that are available.

You've heard from Dr. Rennels about some analyses to try and address whether there is a correlation with the vaccine component or preexisting antibody levels, and there is some suggestion that the amount of antigens and aluminum content in the vaccines may correlate with local reactions, but I

think that overall we have to say that the data are inconclusive.

We do not know the contribution, if any, of cellular immune responses. We do not know if reactions with doses one to four pose a risk for reactions with the fifth dose, and we also do not know whether individuals who have severe local reactions with the fifth dose may be at risk for local reactions with additional doses.

Although pertussis vaccination is not recommended in the U.S. for persons older than age seven, discussions are underway for considering the use of acellular pertussis vaccines in adolescents.

And I will stop there and address any questions.

CHAIRMAN GREENBERG: Thank you, Dr. Farizo.

Dr. Ferrieri.

DR. FERRIERI: That was a very nice presentation.

I have two brief questions. One is by chance, were any of the severe reactions biopsied so that we might understand whether there was vasculitis? Is this an arthus reaction or whatever?

And secondly, do we have any chance have

any animal data on successive immunizations with one of these products and then biopsying of any local reaction seen so that, again, we would better understand the underlying mechanism of the reactions, the severe reactions?

DR. FARIZO: To my knowledge, the answer to both of those questions is no, and the representatives of CLI are agreeing with that, and I don't know for any -- I think the answer is no for the other acellular vaccines as well.

CHAIRMAN GREENBERG: Dr. Estes and then Dr. Stephens.

DR. ESTES: If you look at ethnic groups, is there any difference in their responses with these reactions?

DR. FARIZO: In the data presented today for Tripedia, I think that 96 percent or more of the study participants were white, Caucasians.

DR. ESTES: No, but in previous studies? That was actually why I asked, because the data that's been presented was basically done on a Caucasian population.

DR. FARIZO: In the NIAID study, I think that population is also predominantly Caucasian. I don't think that there have been any analyses, to my

knowledge, any studies which enabled anyone to look at that.

CHAIRMAN GREENBERG: Dr. Stephens.

DR. STEPHENS: I'd like to push the pathogenesis question a little bit further. It almost seems like there are two different groups. One appears to be a severe arthus reaction just clinically, and the other appears to be a different group without much pain, but with a lot of swelling that occurs frequently, and obviously my concern is an IgE mediated phenomenon.

So we really don't know much about the pathogenesis of this process. Is that fair? Does anybody have any data on that?

DR. FARIZO: I think that's fair to say. I think from the clinical picture we really can't distinguish between, for example, a late phase IgE reaction, an arthus reaction, or even a delayed hypersensitivity reaction.

And from discussions I've had with one of our clinical immunologists at CBER, as has been pointed out in the previous question, it would really take biopsies to get at that.

Perhaps there are some additional analyses that could be done looking more precisely at the time

of onset of the reaction, but I'm not sure that with the data available, that we would be able to pinpoint the pathogenesis.

DR. STEPHENS: What about endotoxin content of the vaccines?

DR. FARIZO: For the acellular pertussis vaccines there should be none.

DR. STEPHENS: And that's right; is that?

DR. FARIZO: Yes.

CHAIRMAN GREENBERG: I am still slightly confused as the percentage of children who have severe pain. I know it varied, but that seems to me to be a critical question, and in one case it was one patient and another time it was nine percent and another was two percent.

So if you give this fifth dose to 1,000 patients, what percent are going to be judged to have severe pain, judged at crying on moving a limb?

DR. FARIZO: In the German study in which 580 subjects received the fifth dose, 12 out of 580, or 2.1 percent had severe pain or tenderness, which was defined as crying when the arm was moved. Eighteen percent had moderate pain or tenderness, defined as crying or protesting to touch. That's the largest study we have.

And I think the other percentages you heard were of the children who had large reactions, what proportion of those had pain.

CHAIRMAN GREENBERG: Thank you.

Dr. Kim.

DR. KIM: What about injection sites? Do these severe reactions tend to occur if you give the vaccine to the same site repeatedly or do you have any information on that?

DR. FARIZO: In the studies that you've heard, I believe that the first four doses were given in the thigh, and the fifth dose in the deltoid.

CHAIRMAN GREENBERG: Ms. Fisher.

MS. FISHER: Well, because not 100 percent of the children are having these severe local reactions, presumably this is an interaction between the vaccine composition and the genetic or other differences in the child.

My concern is if it is an IgE mediated phenomenon, again, going back to whether or not -- to study whether or not children who have these reactions are more prone in the future to more severe reactions, more severe, systemic and other kinds of reactions, especially if you're going to be looking at using this, you know, sixth dose in adolescents and also in

adults, it would be important to know, to precisely know, what the interaction is between the vaccine and the host, differences in the host.

DR. FARIZO: I think you raise a good point.

CHAIRMAN GREENBERG: Dr. Ferrieri.

DR. FERRIERI: Dr. Snider had his hand up first.

CHAIRMAN GREENBERG: Excuse me, Dr. Snider.

(Laughter.)

DR. SNIDER: I just wanted to pursue Ms. Fisher's question a little further because you, Karen, had alluded to the fact that perhaps additional analyses could be done, and it seems to me that one of the things that could be done with the data sets we now have is look at those who had larger reactions earlier on and to see if they were more likely to have larger reactions to later doses.

And so if that has been done, I'd be interested in someone commenting on it. If it hasn't been done, I'd be interested in someone saying that they would do it.

DR. FARIZO: I think those are important analyses, but I remind you that the children who

participated in these studies represent a small subset potentially of those who were eligible, and certainly a small subset of the population who received the first four doses.

Remember that in the German study over 12,000 infants received Tripedia, and only 580 received the fifth dose. But still it may be possible to look at some of these questions.

DR. SNIDER: And I think the other issue that you raise perhaps could be looked at as well, which is whether there was some selection bias, because theoretically you ought to be able to look at the distributions in the two populations, the subset and the original group to see if those who had larger reactions earlier on were less likely to get the subsequent dose.

DR. FERRIERI: Ferrieri.

That was exactly my question, but why don't I ask a different one then?

(Laughter.)

DR. SNIDER: I think Peggy was going to answer that.

CHAIRMAN GREENBERG: Peggy, do you have an answer or --

DR. RENNELS: Yes. I have a non-answer.

(Laughter.)

DR. RENNELS: And that is of the 20 -- of the 20 children who experience entire thigh swelling post dose four in the NIAID studies, none of them participated in the fifth dose study. We tried to look.

CHAIRMAN GREENBERG: Could you, because I just can't remember exactly, go over again why we want a fifth dose?

(Laughter.)

DR. FARIZO: Currently recommended DTP vaccination schedule in the U.S. calls for five doses.

CHAIRMAN GREENBERG: So the reason we want one is because we have a recommendation from the bodies that recommend things that we want a fifth one. Those bodies didn't know about this though.

DR. FERRIERI: It's more profound than that. Kathy, why don't you try to answer that?

DR. EDWARDS: Well, I think that the data upon which these acellular vaccines are licensed are efficacy studies that are very important, and I think that one of the issues that we really do need to look at is the duration of protection of those primary efficacy trials, and really critically obviously there are concerns and caveats, as Dr. Livengood has

addressed, but I think that the data that we have seen from those studies in the absence of booster doses is that the protection does seem to be persisting.

So I think that we need to look at those data, to have those investigators come back to us and present the long term duration data so that we can address these new products with the data that exists.

I think that one of the studies that Karen so nicely presented was some data from ICAAC looking at the Lederle study, and what the summary of the data was, that there seemed to be some decline in the immunity, but when you looked at the data they presented, there didn't seem to be a decline.

And when I went up and talked to the investigators, I think that they had initially thought there was a decline, but when they looked at the study more carefully, there wasn't a decline.

So I think that we really need those people to come and present information to us, and maybe we don't -- and actually, someone had brought up a question about, well, what do other countries do, and I think the French have a very interesting approach in that they have decided to give whole cell for the primary.

Now, I don't think that's perhaps a wise

idea, but what they have decided to do is that for boosters that they're giving the acellular booster at the 12 to 15 months, and then they're not giving a fifth dose booster until the adolescent or early adult years, where they really feel that the data suggests that there is a need.

So I think this really does need to be readdressed with the data that we have for the efficacy.

CHAIRMAN GREENBERG: Dr. Ferrieri.

DR. SNIDER: Could I just -- I had some additional comments about the reason for the --

DR. FERRIERI: Well, that's what I was planning to comment on.

DR. SNIDER: I looked back through the ACIP minutes, Pat, to see what was discussed. In 1993, for example, there was a long discussion of why was there a fourth dose and could we drop the fourth dose, and earlier in the '70s there was a discussion of the fifth dose.

And without having the numbers or the slide to show you, all I can say is that the decision about a fourth dose and a fifth dose were based on epidemiologic data as well as immunogenicity data that were available at that time for whole cell vaccines

with the epidemiology of the disease as it existed at that particular time.

So I mean, I would agree with Kathy that it needs to be reexamined, but just to point out that there were epidemiologic findings, and there were immunogenicity issues that seemed to push the experts towards recommending these fourth and fifth doses as they exist today.

DR. FARIZO: Can I also just mention that we also need to remember diphtheria and tetanus, particular diphtheria, when we talk about the vaccination schedule. It's not just pertussis. So that also needs to be considered.

CHAIRMAN GREENBERG: Dr. Ferrieri, you've been waiting patiently.

DR. FERRIERI: No, that's fine. I agree with all of this, and it is not just based on some whim that this has happened. It's based on historical precedence with the whole vaccine.

But the question that I think you could also answer you raised among the unanswered issues, and that has to do with whether or not there's correlation perhaps of the severity of reaction with preexisting antibody levels.

Are those sera not available for analysis?

And has a manufacturer attempted to do this?

DR. FARIZO: In both of the studies, the U.S. and the German study that you've heard about, a subset of children were bled to look at serology. None of those data have been submitted to CBER, but the sponsor may want to comment on what analyses they are planning to do.

DR. MESCHIEVITZ: Yes. I agree. We drew sera on a subset from both trials, and we're analyzing that data now to look at correlations between preexisting and post vaccination antibody titers to determine if there is a correlation with size of reactions.

And I also wanted to quote the last comment in the conclusion section from Mike Pichichero's manuscript, which will be published the first of the year, which stated that the relatively low level of diphtheria antibody in some children prior to the fifth dose supports the continued use of a DTaP booster in this age group.

CHAIRMAN GREENBERG: Dr. Livengood.

DR. LIVENGOOD: I just want to mention that I think the evidence is actually fairly strong that a preschool booster is a good thing in terms of the vaccine. Whether it needs to be the fourth dose

or the fifth dose I think is really an important question that we'll have to disentangle.

And that comes primarily from experience with pertussis in the United States, where approximately five years after the preschool booster, we begin to see middle school outbreaks of pertussis, which are of fairly large magnitude right now.

So I would be concerned that we would potentially be moving the age at which children might have these outbreaks down, and the younger children are more likely to have young siblings at home because I believe the point of the pertussis program is to protect children less than one year of age from pertussis since they're the ones who die if they become hospitalized.

Also, data from the outbreak of diphtheria in the former Soviet Union did suggest that deletion of the preschool booster of diphtheria was somehow one of the really precipitating factors that caused that, and that age group was the group that had the highest attack rate, although not the highest death rate from diphtheria.

CHAIRMAN GREENBERG: We have time for one or two more.

Dr. Peter.

DR. PETER: Yes. The importance of the fourth dose of whole cell was demonstrated in the European trial supported by the NIH, where indeed the protection with three doses of Connaught vaccine was substantially lower, and indeed, the hypothesis was that, indeed, the fourth dose we routinely gave in this country was, indeed, what allowed that vaccine to be effective.

In several studies, population based studies, one in England and another in -- not population, but community outbreaks, one in Michigan, demonstrated that immunity clearly begins to wane after three years.

But this question is critically important because at the very time that we're talking about perhaps that we don't need five doses before school entry, but rather a total of four, we're also considering the use of an acellular vaccine booster in adolescence.

So the follow-up studies are incredibly important, and I really think the dose that's questionable now is the dose that we give between 15 and 18 months. Now, that isn't taking into consideration the diphtheria or tetanus issue.

CHAIRMAN GREENBERG: I'm going to have two

more, and then we're going to take a break. Ms. Fisher and Dr. Huang, and then that's it.

MS. FISHER: Well, in this discussion of vaccine efficacy don't we have to factor in the emerging evidence that the surface protein of the pertussis organism has mutated and the outbreaks that we're seeing in Europe -- and I would say I suppose some of them here -- are due to that fact, that the vaccine is not covering it?

CHAIRMAN GREENBERG: Is there somebody who can answer that question?

Your name?

MS. CHERRY: State your name.

DR. MEADE: Yeah, this is Bruce Meade from Center of Biologics.

I mean, I think those observations from the Netherlands have been published, but I mean, at this point they're epidemiologic observations of two events, you know, changes in a few amino acids and certain proteins, and there's also a similar observation of changes in epidemiology, and the relationship between those two events has not been established at all.

And I know that it's being looked at by the CDC group. The pertussis lab and CDC is looking

at that and what's going on in the U.S., and I think that the relationship between those observations has just not been made in any convincing way yet.

But I mean it's an important observation to be aware of and to be investigating, and it's being done. But, you know, whether or not that is a cause and effect has not been established at all in the U.S. or in Europe to my knowledge.

CHAIRMAN GREENBERG: Dr. Huang.

DR. HUANG: This may be too late to suggest, but in the blood that was drawn from the patients, it would be helpful if you would also just go ahead and do an eosinophil count.

DR. MESCHIEVITZ: I think your comment is partially correct. It is a little late because we keep the serum, but not the whole blood.

CHAIRMAN GREENBERG: Okay. I'm going to take a brief break now because we've had a very good discussion, and what I'd like all of you to do is we'll give you a 15 minutes break. I would like everybody back here at 4:30 to reconvene.

(Whereupon, the foregoing matter went off the record at 4:12 p.m. and went back on the record at 4:32 p.m.)

CHAIRMAN GREENBERG: Okay. We're in the

home stretch. So I'd like everybody to take their seats.

Dr. Farizo, are you --

DR. FARIZO: Are we ready?

CHAIRMAN GREENBERG: Yeah, I'm ready.'

We now have the open public hearing. Is there anybody in the audience who would like to comment on this afternoon's presentation?

(No response.)

CHAIRMANGREENBERG: I'm looking. I'm not seeing.

Okay. I guess there is nobody who wants to make a public comment, in which case we will go on to Dr. Farizo who will present the questions for the committee for discussion.

DR. FARIZO: The first question is: please discuss the safety data submitted to support the licensure of Tripedia for a fifth dose following four previous doses of Tripedia.

The second question is: what, if any, additional studies should be performed?

CHAIRMAN GREENBERG: Well, as Dr. Farizo, said, this is the day when we have questions that aren't questions.

(Laughter.)

CHAIRMAN GREENBERG: But I think the intent here is clear that the FDA wants us to just venture an opinion on how we feel about the safety data and whether it supports the fifth dose or not, and then secondarily whether there's any other information that we like.

What I think I'd like to do is just as this morning open it up for general discussion, and then move through all of you asking for specific answers to the two questions.

So do I have any general thoughts here? Dr. Huang.

DR. HUANG: I'm just a little confused as to whether there are lot to lot variations because Connaught presented a 60 percent swelling in the fifth dose, and Dr. Farizo presented something like 30 percent. I mean that's a difference. Do we know why?

DR. FARIZO: I think the data we presented were consistent.

CHAIRMAN GREENBERG: I thought they were. Between the FDA's analysis, Alice, and Connaught's analysis --

DR. HUANG: Yeah.

CHAIRMAN GREENBERG: -- of Tripedia?

DR. HUANG: They were seeing some 60

percent swelling after the fifth dose.

DR. FARIZO: In the German study?

DR. HUANG: Yes.

DR. FARIZO: Of 580 children?

DR. HUANG: Yes.

DR. FARIZO: Let's see. I can refer you to my slide.

DR. HUANG: I mean they're both high, but it's a twofold difference.

DR. FARIZO: I don't think so.

DR. FERRIERI: What about on page 8?

DR. FARIZO: Mine is slide number 18, and swelling in my slide is 61.4 percent.

CHAIRMAN GREENBERG: And the PMC data was?

DR. HOSBOL: The PMC data was exactly the same. I think what you're looking at is a different cut in subsets of data, moderate swelling versus any swelling and subsets of populations, but the data were --

CHAIRMAN GREENBERG: Phil Hosbol (phonetic), Pasteur Merieux Connaught.

CHAIRMAN GREENBERG: Okay. Other questions?

DR. FERRIERI: Yes. I'd just like to make a comment because I feel maybe it's because of the

cold air blasting in, but my reaction to this is that the Tripedia has behaved very much like other vaccines of its kind, showing the increased reactogenicitywith successive doses, and there may be some percentage differences that overall I guess I'm not struck that it's either more superior nor inferior to other data we've seen.

And I guess I would like us to look at it from that point of view, that we don't understand the reactogenicity of the other ones and likely don't understand the basis of what we're seeing with Tripedia.

CHAIRMAN GREENBERG: Dr. Snider.

DR. SNIDER: I had a question that relates to a comment that was made earlier about the original intention of recruiting 400 people for this study, but now the analysis was based on 96 -- this was the U.S. study, not the German data, and I didn't know what the plans were there. I got confused about whether the study had to be abandoned for some reason or whether there was an intent to continue on.

DR. MESCHIEVITZ: No, no, that's a very good question.

CHAIRMAN GREENBERG: Would you identify yourself?

DR. MESCHIEVITZ: Carlton Meschievitz, again, from Pasteur Merieux Connaught.

The trial recruited a total of 239 subjects, but the recruitment just ended. So we're in the process of analyzing the remainder of that data. The 95 subjects presented are data that have been totally cleaned and quality controlled and submitted to the FDA.

The serious andunexpectedadverse events, however, that I presented did include the entire group because obviously those had come to our attention.

I also had two quick other comments that relate to questions posed earlier, one relative to endotoxin units. The release criteria for Tripedia is 25 endotoxin units per dose, and we routinely run well below that, close to zero.

And secondly, the comment that I made about the diphtheria statement of Mike Pichichero is the version of the paper I had versus the final galley proofs. That statement was deleted. So apparently there's been some trimming of the paper, but a colleague kindly informed me of my mistake.

Any other questions on the --

CHAIRMAN GREENBERG: Dr. Edwards, you had a question?

DR. EDWARDS: Yes. I think it is important to realize that if you look at the data from the other licensed acellular vaccine for the fifth dose, that this is seen with that product as well. So I think that that's important to remember as Pat just pointed out.

The other issue that I do think is important is that there still is not a remarkable increase in the systemic reactions that we're seeing, and these are -- you know, clearly it's an increase in the local reactions, but the other reactions do not appear to be increasing.

CHAIRMAN GREENBERG: Dr. Estes, did you have a question?

DR. ESTES: Just regards to safety data I would have liked very much to have seen some of the analysis of the sera from these children and regarding perhaps IgE specific antibodies to different components in the vaccine. I think in my opinion it's very important that we really understand what is the molecular mechanism or the basis of this reactogenicity, and I'm impressed that it's not clear to me that anyone is really looking at this, and if we're thinking in the future of perhaps another dose, I think that has got to be understood, and I'm hoping

that people really are looking at that.

CHAIRMAN GREENBERG: So you're getting to Question 2.

Any other comments or questions from the committee before I pick on Dr. Kim to start it off? Any other? Anything else?

DR. FERRIERI: Yes. I didn't get to ask this question. So I asked Dr. Farizo whether any analysis had been done on predictors of risk based on having had a moderate or severe reaction after the third or fourth dose that would predict what your reaction would be to the fifth, and that apparently has not been done yet, but certainly could be done and should be done.

And I'm sorry, Harry, if that infringes on Item 2, but I do think that the sponsors need to be very active in looking at some of these analyses.

CHAIRMAN GREENBERG: I agree.

Other thoughts or comments?

(No response.)

CHAIRMAN GREENBERG: Okay. Well, I'm going to start with Item 1, and I think we will have some responses to Item 2 as well, but let's start with Item 1.

Please discuss -- just give me, Dr. Kim,

your feeling about the safety data, and does it support licensure?

DR. KIM: Based on the data presented today, particularly it appears that the data for this product appears to be similar to that of a licensed product presented by earlier. I would think that, you know, I would support the licensure of this product for the fifth dose.

CHAIRMAN GREENBERG: Dr. Snider?

DR. SNIDER: Well, I would agree that the safety data that have been presented to us and hopefully the data on the 290-some once that's analyzed will show that the safety profile of Tripedia is certainly not any significantly worse than the currently licensed -- the DTaP that is currently licensed for the fifth dose, and it certainly appears to be no worse than for whole cell pertussis.

And so our options or the options it seems to me are available are to license Tripedia for this indication or switch to another vaccine that is not demonstrated to be any better or not do a fifth dose.

And not doing a fifth dose, I agree with John Livengood. I don't think the fifth dose is -- the current fifth dose at four to six years of age -- is the one to pick on.

In general I think a lot of us have been talking about concerns about the fourth and fifth dose safety profiles. Our concerns, I think, relate to -- at least my own -- relate to individual children, whether there might be some premonition here of some severe reaction, you know, anaphylactic in nature, but more importantly perhaps has to do with the acceptability of vaccines in general and the desire to have the most favorable safety profile and acceptability.

And so for those reasons, I would support some of the comments that have been made about trying to understand the mechanism of this and devise some strategies for coming up with an even better safety profile for these vaccines.

But I would be in favor of moving forward with licensure based on the safety data I've seen.

CHAIRMAN GREENBERG: Dr. Edwards.

DR. EDWARDS: As I just said a few minutes ago, I think that the comparability of the safety data with the previously licensed product would make me feel comfortable in supporting this.

I think it would be nice to have the serologic data completed so that any correlates of adverse events might be studied prior to the

licensure, and this I would think would be possible to be done.

But I also think it has to be coupled with a critical reappraisal of our entire pertussis vaccination schedule.

CHAIRMAN GREENBERG: Dr. Huang.

DR. HUANG: I completely agree.

CHAIRMAN GREENBERG: Dr. Stephens.

DR. STEPHENS: Yeah. I just want to emphasize two comments. One, I think the data in terms of similarity of adverse events with the other acellular pertussis vaccines is pretty clear, but this whole issue that is really bothersome to me of whether we should be even giving this as a fifth dose is very troublesome, and I think that needs to be at some level addressed.

The other concern is the kind of total lack of interest in pathogenesis. We have a lot of descriptive information about these reactions, but very little in the way of understanding what's going on, and I think there could be potential down the road problems with subsequent doses of these vaccines.

CHAIRMAN GREENBERG: Ms. Fisher.

MS. FISHER: Well, I would agree that the data shows that this is no more reactive than the

other vaccines that are out there, that it's certainly less reactive in terms of its lowered systemic reactions, numbers of systemic reactions, and so I would agree to go ahead and vote for it.

However, I don't think that this, at least my vote, is a vote that in the future that subsequent doses of this vaccine could be given without looking at the molecular basis for these reactions, looking at whether there are certain genotypes who have susceptibility to having reactions and whether previous severe local reactions are a predictor for more serious systemic and other reactions.

I think that you have to look at the pathogenesis, the biological mechanism and nail that before you go any further.

CHAIRMAN GREENBERG: Dr. Estes.

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

CHAIRMAN GREENBERG: So you agree.

Dr. Hartigan?

DR. HARTIGAN: I agree with that, too.

CHAIRMAN GREENBERG: Dr. Ferrieri.

DR. FERRIERI: Well, no data have been presented that indicate any life threatening risks. I think that it's superior to the whole cell vaccine that we used for many, many years, and I think that it

would be punitive to deny licensure of this vaccine without having withdrawal of the fifth dose of any other vaccine. So I support going forward.

But I strongly recommend that we have any post licensure monitoring and a program, a formal program, to better understand, monitor and better understand the issues that many of us have brought up already.

CHAIRMAN GREENBERG: Dr. Peter.

DR. PETER: I agree with Pat and those who have spoken before. I think that the standard has already been set with the whole cell, and we've already licensed one acellular for the fifth dose, and I think this vaccine does as well.

I think the critical questions are, one, the schedule in the first five years of life and whether we need four or five doses and what the timing should be for school entry.

And secondly is I think post licensure studies are important, but particularly with respect to long term epidemiological investigations because, indeed, if we were to determine a need for an adolescent vaccination, we'll need to know what's likely to happen when these children five years from now are candidates for a dose at 12 years of age.

CHAIRMAN GREENBERG: Dr. Livengood.

DR. LIVENGOOD: I generally agree with everything that's been said, and I do think the data support licensure for a fifth dose. From my point of view, if a pediatrician -- if a child came to me, the options would be don't give a fifth dose, and I have expressed my concerns about that, give whole cell, which I would not do, or give the licensed product for this, and I am concerned that there are no data on sort of safety and immunogenicity and efficacy of mixed sequences of these vaccines.

So I really think there's no option for the pediatrician or family practitioner but to give this vaccine for a fifth dose, and I would really think that it would be important to be licensed for that indication.

I do want to mention that as the person who facilitates the ACIP schedule and agenda that the issue of the number of doses needed we'll begin discussion at the February ACIP meeting. I would like to see some attempt to link the persons actually involved in these trials to see what their profile of problems were after the third and fourth doses so we could begin to answer that question, which I think is very important.

If somebody has a reaction after a previous dose, I think it would be very important for us to see whether or not we need to contraindicate further doses or not.

And I'm a little concerned about what I perceive to be a lot of emphasis on the part of persons to move to adolescent immunization with acellular pertussis products when all of the data will be with children who have had their primary series with whole cell at the time it's licensed that will get into a similar situation five years, six years further down that if we don't really make an attempt to try to look at these very important issues now.

CHAIRMAN GREENBERG: Dr. Myers.

DR. MYERS: I agree.

CHAIRMAN GREENBERG: Well, I agree, as well, and I would simply say again that as I understand it, in the second quarter of the year 2000 one heck of a lot of people are going to begin to get their fifth dose. That provides the opportunity to get samples and prospectively start studying those people because they're going to be available for a sixth dose in X number of years, and if you don't start now we won't have the specimens.

So all of that needs to be thought through

relatively quickly because those doses are about to be given. So I vote I'm in support.

And now I'm just going to go on to the second item, which we've covered in part, but I'll start again with Dr. Kim.

What, if any, additional studies should be performed?

DR. KIM: Again, some of these issues have been mentioned previously, but just for, you know, documentation I would rephrase some of the issues that have beenindicatedthat require further investigation that include the basis of reactogenicity with the subsequent doses of acellular vaccines should be done, along with a duration of protection that will be very important that pretty much will determine whether subsequent doses of acellularvaccines would be needed or not.

And then I guess I forgot to ask this question earlier, but there was some issues about the selection bias, whether, indeed, individuals who, indeed, had several reactions may not be a participant in subsequent studies.

So I guess it may be interesting, again, a Harry indicated that subsequent to the licensure, that post licensure survey should include those

studies for these vaccines, but the vaccine which has been already licensed for the fifth dose, I would be interested in knowing whether, indeed, there's any information available on that particular aspect, that individuals who have received fifth dose, regardless of the nature of previous reactions, indeed, was there any trend toward more reactions with individuals who had some reactions with the previous vaccines.

I don't even knowwhetherthat information is available from the FDA, certainly not from the sponsor for Tripedia, but you know, the manufacturers.

DR. MESCHIEVITZ: Carlton Meschievitz, Pasteur Merieux Connaught.

I just wanted to mention we are committed to doing post licensure study. We have a birth cohort of 5,000 children in Seattle that we're following along through multiple doses of vaccine. So we'll be able to follow multiple birth cohorts, and obviously we're committed to looking for the usual types of reactions and more carefully characterize the actions that were described today.

CHAIRMAN GREENBERG: Thank you.

Dr. Snider.

DR. SNIDER: Looking at the question, I wonder if it was constructed in the context of what

additional studies should be performed before licensure or whether it is wide open in terms of what would you ever do down the line.

I'm assuming it's the latter because we've all been responding that way, but with regard to the more restricted issue, I'm not sure any additional studies need to be done, but I just would again call attention to the fact that there are data to be analyzed and would anticipate that those data would be analyzed and reviewed by FDA since I would think that that could be done in a reasonably short period of time.

with regard to the additional studies, there are a whole litany of studies that have been outlined. We've indicated our interest in knowing whether people who have these large local reactions, what the mechanism is or whether there's a variety of mechanisms, whether those people who have larger local reactions are more likely to have large local or even larger local reactions in the future.

A lot of issues have been brought up about the use of different types of DTP vaccines, mixing those issues, and there are the issues about the duration of protection with acellular vaccines and the optimal schedule.

I think all of those things are important to think about. I would point out that there's no agency or organization that has clear responsibility for doing vaccine safety studies, and so resources for doing that kind of thing are rather limited.

So in reality some priorities have to be established for which ones of these things actually can be done and funded by different entities, and some choices will have to be made and tradeoffs have to be made because of the limited resources for looking at vaccine safety.

CHAIRMAN GREENBERG: Dr. Edwards.

DR. EDWARDS: I think in addition to what's already been said, which I won't say again, there are some additional sera that are available from the NIH trial both at the primary series, the fourth and the fifth dose booster that could conceivably be looked at particularly with the patients that had the severe swelling. So I think that is frozen and IgEs and amounts of antibody and those things certainly could be done with sera that exist.

There is also a little more data about the mix and matching and mixed schedules because those were part of the NIH studies. So there may be some data that would look at whether the mix schedule --

there are certain aspects of the mix schedule that would be more problematic, and I think that could perhaps be dissected out, although, again, the numbers are somewhat small.

And then I also think there are some studies that are being funded by other companies that are looking at mechanisms. I think that there perhaps is more being done in terms of investigation than we're sort of privy to at this point.

CHAIRMAN GREENBERG: Dr. Huang.

DR. HUANG: Besides being interested in the mechanism of the swelling and erythema, obviously one would like to have a better vaccine. I mean we're settling on this because all of them seem to do the same bad thing, and we've accepted some of them, and so we have to accept this one as well.

And it would be nice to take whatever hints that we have, that if reducing the total amount of antigen or reducing the aluminum would be useful, those are certainly a direct thing to focus on.

CHAIRMAN GREENBERG: Dr. Stephens.

DR. STEPHENS: Yeah, I think most of the points that I wanted to make are made.

I would like to ask the manufacturer a couple of questions. One, you mentioned that there