U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

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PUBLIC HEALTH SERVICE

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS

ADVISORY COMMITTEE

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Tuesday, 14 September 1999

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The meeting took place in Versailles Rooms I and II, Holiday Inn, Wisconsin Avenue, Bethesda, Maryland, at 1:00 p.m., Harry B. Greenberg, M.D., Chair, presiding.

OPEN

PRESENT:

HARRY B. GREENBERG, M.D., Chair

NANCY CHERRY, Executive Secretary

ADAORA ADIMORA, M.D., Member

ROBERT S. DAUM, M.D., Member

KATHRYN M. EDWARDS, M.D., Member

MARY K. ESTES, Ph.D., Member

WALTER L. FAGGETT, M.D., Member

BARBARA LOE FISHER, Member

DIANE E. GRIFFIN, M.D., Ph.D., Member

ALICE S. HUANG, Ph.D., Member

KWANG SIK KIM, M.D., Member

DIXIE E. SNIDER, JR., M.D., MPH, Member

DAVID S. STEPHENS, M.D., Member

ROBERT BREIMAN, M.D., Invited Participant

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

DAVID KARZON, M.D., Invited Participant

I-N-D-E-X

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

1:00 p.m.

CHAIR GREENBERG: Could people in the back please take their seats? Peter Paradiso, sit down.

Okay. I'd like to welcome you all to the Vaccine and Related Biological Products Advisory Committee. My name is Harry Greenberg, and after the welcome I'd like the members of the committee to briefly introduce themselves and their affiliation, and we can start over here.

Rob?

DOCTOR DAUM: I'm Robert Daum from the University of Chicago.

DOCTOR EDWARDS: I'm Kathy Edwards from Vanderbilt University, Nashville, Tennessee.

DOCTOR ADIMORA: Ada Adimora, University of North Carolina at Chapel Hill.

DOCTOR KIM: Kwang Sik Kim from Children's Hospital in Los Angeles.

DOCTOR GRIFFIN: Diane Griffin from Johns Hopkins School of Public Health.

DOCTOR SNIDER: Dixie Snider, Associate Director for Science at the Centers for Disease Control and Prevention.

DOCTOR STEPHENS: David Stephens, Emory

University, Atlanta.

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

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

CHAIR GREENBERG: Harry Greenberg, Stanford University and the Palo Alto VA Hospital.

DOCTOR KARZON: David Karzon at Vanderbilt Medical School.

DOCTOR HUANG: Alice Huang, California Institute of Technology.

DOCTOR FERRIERI: Patricia Ferrieri, University of Minnesota Medical School, Minneapolis.

CHAIR GREENBERG: Okay, thank you.

We have a couple of new members of the panel. Welcome.

And, without further ado I'd like Nancy Cherry to read the COI statement.

EXECUTIVE SECRETARY CHERRY: Good morning. Let me add my welcome to all of you. We haven't had a meeting for a while, but particularly also to our new members, Doctor Walter Faggett who isn't at his place yet, Ms. Barbara Fisher over here on the corner, Doctor Diane Griffin and Doctor David Stephens. Their terms of office began in February, but since we

haven't met face to face since then this is their first meeting.

Two of our members, Doctor Steve Kohl and Doctor Dianne Finkelstein, are unable to attend this meeting, but the Director of the Center for Biologics Evaluation and Research has appointed Doctors Robert Breiman, Theodore Eickhoff, Patricia Ferrieri and David Karzon as temporary voting members for Sessions I through V and Session VII. Doctor Eickhoff will not be able to join us until tomorrow.

The committee management specialist for this meeting is Ms. Denise Royster, and you probably saw her at the table or here in the room. She's assisted today by Ms. Rosanna Harvey, who we borrowed from another committee.

And now, may I have a drum roll, what you've been waiting for, the conflict of interest statement.

The following announcement addresses conflict of interest issues associated with this meeting of the Vaccines and Related Biological Products Advisory Committee on September 14-15, 1999. To determine if any conflicts of interest existed, the agency reviewed the submitted agenda and all financial interests reported by the committee participants.

In accordance with 18 USC 208, the following individuals have been granted waivers that permit them to participate in the committee discussions: Doctors Edwards, Greenberg, Griffin and Ferrieri. Doctor Greenberg has recused himself from the discussion on RotaShield, and Doctor Mary Estes has received a limited waiver permitting her to participate in that same discussion by sharing her expertise. Should the need for votes arise during that session, Doctor Estes will be unable to vote.

Several participants disclosed a potential conflict of interest, which was deemed by FDA as not requiring a waiver, but does suggest an appearance of a conflict of interest. A written appearance determination under 2635.502 of the Standards of Ethical Conduct has been granted to permit Doctors Daum, Finkelstein and Stephens to participate in the committee discussions.

With regard to FDA's invited guests, and this is tomorrow, the agency has determined that the services of Doctor George Carlone is essential for the discussion of meningococcal conjugate vaccines. Doctor Carlone reported that as a part of his federal government duties he is involved in a CRADA for pneumococcal protein vaccine, supported by a firm that

could be affected by the discussion.

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

With respect to all other meeting participants, we ask in the interest of fairness that you address any current or previous financial involvement with any firm whose product you wish to comment on.

Copies of all waivers and appearance determinations addressed in this announcement are available by written request under the Freedom of Information Act.

And, I have one other little announcement. Some of you may need to move your microphones just a little closer. I think it will help our transcription.

CHAIR GREENBERG: Thank you, Nancy.

We have an interesting and full agenda for this afternoon, so I'd like to, without further ado, move on, and Doctor Bill Egan from FDA is going to update the panel and the audience on the issue of

Thimerosal and its inclusion in various vaccines.

Bill – all the speakers should realize we have a strict time limit, and I'd ask you to end your talk before it.

DOCTOR EGAN: Good afternoon.

Over the past several months, there has been a significant amount of activity related to Thimerosal as a preservative in vaccines. During the next few minutes, I hope to provide you with an overview of these activities and a sense of where we are headed.

Let me first provide a little background about preservatives and Thimerosal, and I should first mention that most of the data and the listings that are in my talk were compiled by Doctor Leslie Ball, Doctor Doug Pratt and Doctor Robert Ball.

By way of background, let me mention that a preservative must be present in multi-dose, multi-entry vials. This requirement was placed into the Public Health Service regulations in 1968. There were, and there still are, good reasons for this requirement, for a preservative in these multi-entry vials.

The regulations, our Code of Federal Regulations, also state that a preservative should not

be toxic to the recipient, and it should not denature the product.

A definition of a preservative, however, is not provide in the Code of Federal Regulations. A definition, however, is found in the United States Pharmacopeia, and is widely used. Although CBER and the Office of Vaccines has always accepted materials that meet the requirements of the USP definition, we are not bound to follow that definition.

Thimerosal is the most widely used preservative in vaccines, and has been in use since the 1930s. It was first introduced into this diphtheria toxoid by Eli Lilly. It is currently present in about 50 U.S. licensed biological products in concentrations ranging from 0.003 to 0.01 percent. Thimerosal use was reviewed internally within then the Bureau of Biologics in 1976, and it was concluded that there were no harmful effects of Thimerosal at the doses that were received during a lifetime.

I'd also note that Thimerosal, which is a mercuric derivative with ethyl and thiosalicylate – attached to it, and it breaks down the ethyl mercury and thiosalicylate.

The Food and Drug Modernization Act of 1997 mandated that FDA compile a list of mercury-

containing products and subsequently conduct an analysis of the effect of mercury on recipients of these Thimerosal containing or mercury containing products. The product listing is due to Congress in November of this year. There is no stated deadline for the analysis of the effects.

Now, independent of the FDA Modernization Act, there has been a concern in various corners, including CBER, of the increase in accumulated amount of mercury that children are receiving through vaccines. At FDA, we have been discussing this issue with manufacturers and have requested them that as new products are developed that they not contain Thimerosal unless absolutely necessary.

A number of U.S. licensed vaccines contain Thimerosal, and these are presented on the next two slides. These vaccines include DTaP, all the DT&Td products and hepatitis B and a variety of additional vaccines, including influenza, meningococcal polysaccharide vaccines, and rabies vaccines.

There are, however, a number of vaccines that are Thimerosal free, either by virtue of presentation in single-dose images, or through the use of alternative preservatives. These vaccines include some DTaP, for example, Infarix, HIB vaccines, HIB

hepatitis B combinations, Comvax, IPV/OPV, MMR, et cetera.

However, we are still left with several vaccines for which there is no Thimerosal free presentation, and these include the whole cell containing pertussis vaccines and the toxoid vaccines, the diphtheria and tetanus toxoid vaccines.

One can calculate the maximum exposure to Thimerosal that a child might receive by age six months or by age two years. Excluding the pediatric use of influenza vaccine, the total, the maximum amount received is 187½ micrograms by six months, and 237 micrograms by two years of age.

Through the use of particular vaccines, however, this exposure could be reduced to zero, as is presented on the next slide and is in your handouts, by judicious choice of schedule and vaccines, with the exception of, perhaps, influenza if that's needed, one could have a completely Thimerosal free schedule.

Now, the question remains as to the level of risk, that even the maximum exposure to Thimerosal containing vaccines might pose. At the outside in a state that there is no data to think that this exposure to Thimerosal presents any risk, nonetheless, when we present the current U.S. guidelines for

exposure, and I use the plural because there are more than one, the EPA guidelines approximately 0.1 microgram per kilogram per day, the ATSDR 0.3 micrograms, the FDA guideline 0.4. There's also a WHO guideline, which is 0.47 for adults and 0.1 micrograms per day. These are given as weeks, so just divide by seven.

Now, using these numbers, the suggested limits on methyl mercury intake, for the first six months for different birth cohorts in infants can be calculated, this is on the next slide, and one can see that for all birth cohorts, weight cohorts, the vaccination schedule would exceed the WHO guidelines and EPA guidelines, barely exceeds the ATSDR guideline at the lowest five percent birth weight, and does not exceed the FDA guideline. And, by two years of age it's not exceeding any one of these guidelines.

Now, there are many caveats to using these recommendations, and this includes, you know, is methyl mercury as toxic as ethyl mercury, routes of administration, dose schedule, magnitude of doses, pharmacokinetics, the rate of elimination and so on.

Let me now discuss what's been happening over the past several months, keeping these background data in mind. The most significant event was the

AAP/PHS joint statement that was issued on July 7, and these groups agree that, "Thimerosal containing vaccines should be removed as soon as possible." The groups also recommended that, "Clinicians and parents can take advantage of the flexibility within the existing schedule to postpone the first dose of hepatitis B from birth until two to six months." There was no change in the recommendation to immunize infants for hepatitis B surface antigen positive mothers.

The joint statement also called for a formal request from FDA to the manufacturers for a plan to reduce or eliminate Thimerosal from their vaccines, a review of pertinent data in a public workshop, expedited FDA review of manufacturing supplements for removal of Thimerosal, additional studies to understand the risks of Thimerosal, monitoring changes in immunization practices, and to provide better information to health care workers to enable them to better communicate with parents and consumer groups.

Many of these recommendations have already been implemented. FDA issued its letter to the manufacturers on July 1, actually a week in advance of this statement, and the letter asked manufacturers to

provide plans for removing Thimerosal, if they intend to remove Thimerosal, or if they plan on keeping Thimerosal an explanation for this decision.

Manufacturers have responded to the FDA letter. Additionally, through PhRMA, the vaccine industry "supports the goal of Thimerosal free vaccines and is working closely with FDA and other government agencies, as well as the American Academy of Pediatrics, to meet this objective." A public workshop was held on August 11th and 12th at the NIH, and data related to Thimerosal use and safety were reviewed. And finally, Merck submitted a supplement for Thimerosal free hepatitis B vaccine and this was approved on August 22nd. It was reviewed expeditiously.

The final issue is where are we going, and I think that Thimerosal will be removed from most, if not all, vaccines, and the alternative of choice, at least in the United States, will probably be single dose presentations. Alternative preservatives will also be used, but we need to consider increased toxicity testing for these, so that we don't get in the similar position that we were with Thimerosal, and, perhaps, we might – we should allow, or might allow, a decreased effectiveness relative to the

current USP requirements for vaccines as preservatives, which are rather stringent requirements.

Thank you.

CHAIR GREENBERG: Thank you, Bill.

Can we have some lights?

Well, we are doing very well here.

This is, obviously, panel members, an important and high public visibility issue. Bill has presented this very brief review to keep us appraised of what's going on, but I think we have a time for a few questions if any of you have them.

Dixie?

DOCTOR SNIDER: Well, I just want to add to what Bill has said, bringing us up to date, he mentioned that the AAP/PHS statement talked about postponing the hep B dose, and on Friday the MMWR, taking the approval that Merck proceed for their hepatitis B vaccine, CDC issued some new recommendations to use the Thimerosal preservative free vaccines to vaccinate infants at birth. The reason for that, some of which was given in the MMWR article, is that there's a lot of confusion, and many hospitals had discontinued hep B vaccines at birth altogether, even for infants of high-risk mothers,

including those that were known to be hepatitis B positive. So, we felt it important to restart the infant hep B immunization with the Thimerosal free product.

People can read the article for further details.

DOCTOR EGAN: Yes, thank you very much for adding that point, which slipped my presentation.

CHAIR GREENBERG: Thank you, Dixie.

Actually, that's heartening, because that was a problem, and, clearly, no matter how clear you try to be the public and physicians were confused by this issue, and evidently some high-risk children were not vaccinated when they should have been.

Any other –

DOCTOR FAGGETT: Harry, Walter Faggett, Chairman – Section NMA.

One question about the Merck vaccines, what kind of inventory do they have, how available is it going to be for immunizing those children in the nursery?

DOCTOR EGAN: Yes. I can't comment on the current inventory of Thimerosal free vaccine in Merck, but if somebody is here from Merck that knows that answer?

DOCTOR FAGGETT: We had a meeting in Vegas in August, it was a fact that it is very confusing to our patients and parents, and I don't know if you emphasized the fact that in our present situation we need to really also be cautious about vaccinating premature, low birth weight infants. I mean, that was another issue that was brought up.

So, those are two issues that we need to have some clarity on. Would the Merck vaccine be used on low birth weight and pre-term infants as well? That's going to be another –

DOCTOR EGAN: I think that may be in the MMWR article but I'm not sure. Dixie, do you know how that's addressed in the MMWR?

DOCTOR SNIDER: I don't recall that we addressed the low birth weight issue. It's clear that for a while, Walter, we're going to be in a position of having both Thimerosal preservative free vaccine and Thimerosal containing vaccine on the market, and these guidelines basically are saying, let's give preference to the younger children for the Thimerosal preservative free, and use the Thimerosal containing products for the older children and adults, because there will be both, and there will be supply problems initially.

I can't speak as to what the supplies are, but I know that Merck is working very hard to make as many doses available as they possibly can safely, and it shouldn't be too long before we move to a situation where we — one thing I didn't mention is that Smith Kline-Beecham is also in the process of making a preservative free, their hepatitis B vaccine preservative free, so we are in an interim period now, hopefully, we'll get to a period where we have no hepatitis B vaccine that contains Thimerosal.

As far as low birth weight infants are concerned, I don't think that this last MMWR addressed it. There certainly is greater concern with low birth weight infants, premature infants —

CHAIR GREENBERG: Excuse me, can you speak a little closer to your microphone?

DOCTOR SNIDER: There is greater concern with low birth weight infants, with regard to mercury, and there's been a lot of discussion about what to do about those infants. I think the fact that we now have preservative free vaccines available should help alleviate those concerns.

CHAIR GREENBERG: Doctor Huang?

EXECUTIVE SECRETARY CHERRY: Before we go any farther, would all of you hold your microphones a

little close, because there's a buzz in here and I think people in the audience are having trouble hearing.

DOCTOR HUANG: As a point of information, is there a cost difference to the consumer between Thimerosal free and Thimerosal containing vaccine?

DOCTOR EGAN: I don't know how they are being costed. I'm not aware that there's any change in costs to the CDC for their NIP program.

DOCTOR HUANG: Is there a difference between single and multi-dose vaccine?

DOCTOR EGAN: Yes, I mean, general single dose presentations are more expensive. But, you have to know that all of the single dose presentations of hepatitis B, for example, contained Thimerosal as well, and this was so that there would be a single formulation that the manufacturers would have that would go either into single-dose vials or multi-dose vials.

CHAIR GREENBERG: Doctor Daum?

DOCTOR DAUM: Close enough to the microphone, I hope.

The American Academy of Pediatrics, at least currently, does not have a recommendation for immunizing newborns less than two kilos, so I don't

know whether that situation is going to change with Thimerosal free, but I think it probably will have no impact on that situation.

I think that it should be noted somewhere during this discussion that this is going to have some impact on places where money is more scarce than it is in the United States, because it really is the end of multi-dose vials if other countries decide that they want to remove this preservative from their products as well. And, this was an important point, I thought, raised at the NIH workshop by people concerned with health care beyond the United States.

I would be a little remiss, I guess, if I didn't comment on the Academy of Pediatrics and the Public Health Service, the speed and the aggressive nature of changing the recommendation so quickly. It seemed that FDA had set in motion a fairly orderly review of Thimerosal containing products, and it seemed that plans were going forward to decrease them in products or to eliminate them.

Thimerosal has been around and used for a long, long time, and one wonders what the need was to act so quickly, an issue this urgent, reversal of direction, which I think did confuse a lot of people.

At the workshop, Barbara Watson from

Philadelphia commented that at her hospital there was at least three children that she knew of that were born to serotype positive mothers, who were not immunized at birth because it was believed that this vaccine shouldn't be used in that context incorrectly.

I also, one more comment and then I'll end with a question for Bill. I also think it might be instructive for people to know that there are other impacts, it turns out, of changing or deleting that birth dose, which, again, made me concerned about the speed with which the recommendation was changed. We have a paper in press at JAMA which will be coming out the first week in November, which documents in the inner city of Chicago that that birth dose, first dose of hepatitis B does something very positive to people, that it makes it more likely that they are going to end up at two years of age up to date with all of their shots.

If you stratify our inner city population by those who received that first dose and those who didn't, at two years of age there's an impressive and statistically significant difference in who is up to date for all shots, DTP, IPB, everything. So, I view the suggestion to postpone that first dose with some special concern, perhaps.

And, I want to end with a question, Bill, if you don't mind, after all those comments, is how is FDA viewing manufacturers' applications to just remove the Thimerosal? It sounds like you went very quickly with the Merck product, but can a vaccine that's been licensed, safety and immunogenicity profile in place, turn around and remove the Thimerosal and there's an assumption that everything else would stay the same. Is that the approach, or is there some other?

DOCTOR EGAN: Yes, well, that's a very complicated question, and one that Doctor Baylor tried to address as best he could during the Thimerosal workshops. For a more complete answer, I would refer people to that when it becomes available on the web.

There are a lot of issues. It depends whether Thimerosal is in the product or whether it's contained in the diluent for the product.

What the expectations are and what data may already exist from the manufacturers with regard to stability, it does not mean that Thimerosal per se, you know, lengthens the stability or decreases the stability of the hepatitis B vaccine at least, and there are some data that do address that. I mean, certainly, although not perfect, there's data, for example, on Comvax, which is a Thimerosal free

preparation, and, you know, the hepatitis B component is not adversely impacted by not having Thimerosal in that preparation.

There are many other issues, for example, if usually puts material in single-dose presentations with a preservative, then the issue of, you know, the ability to manufacture and to put material into single-dose preparations without a preservative, you know, and maintain sterility, that has to be assessed, because the last thing you want is, you know, material that's no longer sterile.

For some of the other vaccines, how crucial they may, for example, in influenza manufacturing to maintain some Thimerosal during the manufacturing, I think we'll have to look at that. So, it becomes an awfully complicated situation, Merck being one of the simpler.

CHAIR GREENBERG: Any other — Ms. Fisher?

MS. FISHER: Thank you.

Well, I think the FDA acted very prudently in asking the manufacturers to take the mercury out of the vaccines at this point, as there is accumulating evidence, for example, the study in the American Chemical Society here this month that mercury can circumvent a blood brain barrier that usually prevents

such toxins from entering the brain.

As the mercury free vaccines are coming out, and we also will have the vaccines that have mercury in it, hepatitis B vaccines, should consumers be asking, Doctor Snider, should consumers be asking their pediatricians for the mercury free vaccine, especially for premature infants and two-month old infants?

DOCTOR SNIDER: I think if you look at the MMWR, hopefully, the impression you will come away with is that we are urging providers and parents of infants who are to receive the birth dose to receive the Thimerosal free product. So, I think we are, although I think we addressed our MMWR primarily to providers, but certainly I think it would be appropriate for parents to request the Thimerosal free product for that particular age group.

But, I mean, there is a caveat with that, in that if there is none available, and you have a mother whose status you don't know, or who is known to be hepatitis B surface antigen positive, you don't want to have that infant become infected with hepatitis B and have the high risk of cirrhosis or cancer. So, you know, there you take the greater risk by not vaccinating with a Thimerosal containing

product.

CHAIR GREENBERG: Any other questions?

DOCTOR FAGGETT: Harry, just one other comment.

Back to Dixie's point, I think this brings up the issue of making sure that whatever information that pediatrician or family practice doctor has to tell the parent is accurate and up to date. The NMA fully agrees with AAP position, but we really need to look at how we are informing the information we are putting out there, because that's back to the question of inventory, to raise parents' expectations that they can get it and not have the inventory, I think, does not serve anybody well.

CHAIR GREENBERG: Well, I think those comments are excellent. I would just like to say for everybody who was not at the two-day conference that I think the FDA, and the AAP, and other bodies, are to be commended on trying to bring order to what is inherently a very complex database, and it is not critical to really understand this in scientific terms, and it is not – there is conflicting scientific data that on the face of it looks like it was obtained correctly as to the risks, and there's clear-cut advantages. So, I think the FDA is to be commended,

as is Merck for moving very rapidly for eliminating Thimerosal in a product that is not needed.

On the other hand, for sure a mother who is infected with hepatitis B virus, that infant should be vaccinated, and that's a clear risk that we don't want – that we want to deal with.

I'd like to thank you, Bill, for updating us, and now we are now still ahead of time. I'd like to move on to our next agenda item, which is Doctor Andrew Lewis, there he is, and Doctor Lewis is going to update us on the cell substrate workshop. I think you all remember that I guess it was last year Andy spent some time bringing us up to date on the very important topic of cell substrate selection.

DOCTOR LEWIS: Thank you, Doctor Greenberg.

Just to introduce myself, I'm Andrew Lewis, in the Office of Vaccines, Division of Viral Products, and I'm going to attempt to review for you, in fairly cursory detail because there's a huge amount of information that was presented, the cell substrate meeting that we had last week, mid Friday afternoon, late.

I think the beginnings of this meeting started before this committee on November the 19th last year, when we presented or introduced the topic

of using aplastic cell substrates for viral vaccine development and manufacturing to the committee.

Keith, can I have the next overhead, please? Just to review very briefly for those of you in the audience and on the committee who were not present at that meeting, the motive antifactors that are driving the Center for Biologics to consider using neoplastic cell substrates for viral vaccines include, very importantly, development of whole virus, the traditional vaccines to HIV, and in addition several other things are very actively involved in generating this need.

Bioengineering approaches to viral attenuation are creating large opportunities to develop vaccines that had not been available to us previously. Emerging viruses, such as the Hong Kong influenza H5N1 flu strain, and now I think more recently H9 and 5 flu strain may require rapid attention. Progress in understanding carcinogenesis has been very rapid in the past decade, and along with that our ability to detect and identify adventitious agents. And finally, we have a very successful experience since the late 1980s with using highly purified biologicals that were made and actually derived the neoplastic cells.

So, based on these factors, there is increasing interest and need to use neoplastic cells to develop traditional vaccines.

Now, as a result of our presentation before the committee last year, several things evolved. First, we were going to develop a document outlining issues. We were going to hold a workshop on those issues and on this document, and I think these are the first two things that we have accomplished, and we're at this stage in implementing the approach that we've outlined on this overhead.

The document, we estimated last year it will take us about six months to put together. We had the document ready, I think, some time in May for internal review, and then it went out to the people who were going to be addressing the topic in July. And so, that document sort of formed the basis for the agenda for the meeting, and I'll have a little bit more to say about that.

The title of the meeting was, "Evolving Scientific and Regulatory Perspectives on Cell Substrates for Vaccine Development." The meeting was sponsored jointly by the Center for Biologics, the International Association for Biologicals, and the National Institute of Allergy and Infectious Diseases,

the National Vaccine Program Office, and the World Health Organization.

The goals of the workshop were two in number. First, to identify the concerns and issues that were associated with using neoplastic cell lines, and then to identify approaches to determine the levels of risk that might be association with those concerns.

The meeting was organized around the following scheme. The first session was to introduce the cell substrate history and to review the milestones in cell substrate development over the past 50 years, and then following that review process to present the CBER draft proposal as it formed the basis for the need for the meeting, number one, and for the organization of the session. The other sessions were then organized around the concept of issue presentation, each specific session followed by a panel/audience discussion about issues, and we proceeded through that on that through the three-and-a-half days of the workshop, with one exception, that was a session on Thursday night designed for people to present late breaking information and miscellaneous topics that the speakers and people who had been contacted to participate in the meeting felt like that

they would be able to – that would be of interest to the audience.

I won't have anything more to say about that session, as it was a composite of a lot of topics that were germane, but that really did no get involved in the business of the panel discussions to any significant degree.

Now, the topics of cell substrate history were reviewed very nicely by Doctor Elwyn Griffiths, and Bill Egan, and Leonard Hayflick interacting during the first three presentations Tuesday evening, and following that Doctor Phil Krause and I took about an hour of the session's time to present the approach that CBER had put together, based on the presentation that was made before the committee last November. And, that approach was developed in this document.

The document is on – will be on the CBER web site very shortly, and copies of it will be made available to those people who are, in fact, interested in receiving that.

As I said, we distributed copies to the speakers and the session panel chairs who were going to be addressing the contents of the document during the course of the workshop.

The table of contents, very quickly,

includes these particular items. I think it covers some 25 or 30 pages, and we took the suggestions of the Advisory Committee to – and expanded on the approach that we presented before you last November, and I think based on the comments that we got it is reasonably comprehensive.

The gist of the document revolves around the concerns that were outlined again for the committee last November, and just very quickly for the audience and to recapitulate a bit. It's two comprehensive – it's too extensive to be presented on one slide, but the concerns as we have identified them represent tumor cell contamination, adventitious agent contamination, cell DNA contamination, cell protein contamination, viral-viral and viral-cellular interactions. The represent the generation of recombinants or reassortants, or – of the transduction cellular genes that might take place when vaccines are produced in the aplastic cell substrates. And then finally, the issue of genomic instability.

So, this particular – the sessions of the workshop were organized around the concerns that were listed in this paper. I think you'll see that as we go through the sessions. And finally, we tried to bring the CBER folks together with an algorithm which

we are calling a defined risk approach algorithm, and in this particular algorithm we are attempting to develop a systematic way of getting at the levels of concern or the levels of risk, however you want to call it, that might be posed by each of the issues that was in that table. And, just to again recapitulate what we would hope to do, with more or less success based on available data, is to assess the level of risk posed by each of those concerns and issues quantitatively. We would hope to be able to establish in many cases the probability of a worst case scenario for each of the issues or concerns, and then using these data to evaluate the levels of risk individually and cumulatively, and then finally, based on this data set, to assess the relative risk of the product.

Now, as I've already covered session one, we'll start with session two of the meeting that occurred last week, the session was Wednesday morning, and the task of the session was to review the mechanisms of neoplastic development in carcinogenesis, and to assess the impact of the issues posed by the use of neoplastic cells as vaccine substrates.

The basic topic here was the possibility

of the increasing recognition that the neoplastic process is a multi-factor process. It takes a multiplicity of events, and this has been a very recent paper in Nature that came out of Doctor Weinberg's laboratory at MIT, which demonstrated rather conclusively that at least three to four separate genetic alterations are required in normal cells before they'll evolve into a neoplastic cell which is capable of forming tumors.

And, the idea was to explore this multi-factor process with the concept of what the implications of this were for vaccine safety. And, the consensus that emerged from the panel that considered the topic after the session, after the relevant data was presented, basically was that due to the multi-factor processes that produce neoplasia, neoplastic cell components, which include nucleic acids and cell proteins that might remain in vaccines, should pose little or no risk of transferring neoplastic activity. And the second consensus that we feel emerged from this discussion was that there's really no correlation between the degree of aggressiveness in neoplastic cells and the ability to transfer neoplastic information to other cells.

Now, I would hasten to point out that

these were – this consensus was based on opinions of the panel and they readily expressed the fact that there's not a lot of data out there that sustains some of these opinions, and therein lies a problem that we have with trying to make some of the levels of risk assessment that we would like to make.

The second session, I don't think we cheated a little bit, we moved the business of viral-viral and viral-cellular interactions into the second session because this was the most complex, I think, of the issues that we asked the workshop to address. These represent a multiplicity of events that occur at low frequency in cultures where the multiple viruses are replicating at the same time, and these interactions include recombination, reassortant, deletion, repair, pseudo typing and transduction of cellular DNA or cellular nucleic acids to other types of cells by way of a virus that may incorporate this material during this – cycle.

And, since this was a fairly extensive topic, it occupied two independent sessions of the meeting, and the consensus that emerged from the panel that considered this was that these types of interactions are quite low-frequency events, and that the type of interaction that will occur will, of

course, depend on the virus substrate combination. Different types of viruses, whether they be a DNA virus, or an RNA virus, combined with a particular substrate will determine whether these types of interactions will occur, and, in fact, at what frequency at which they may occur.

The third consensus was that novel agents of unpredictable pathogenicity can arise from these types of interactions under experimental conditions. Exactly what type of agent that might arise under manufacturing conditions, of course, is purely speculative at this point in time.

And then finally, the panel felt like the primary cells, in fact, owes, perhaps, a greater risk than tumor cells for the occurrence of these type of events, simply because primary cells each batch is different and each batch would have its own unique infectious or latent agent that might be involved in these types of interactions. Therefore, it would be much more difficult to get a handle on that, and you'd have to try to assess that every time, with each batch of primary cells, rather than being able to do it once and have some assurance that you will not see the introductions of something new by going out and getting a whole new cell culture system.

And finally, they recognized that unrecognized and unknown agents, perhaps, represent the most significant concern that one has to deal with in this type of situation, and in this regard they sort of preempted the work of a later panel.

In session four, the task was to review the issues associated with residual DNA of neoplastic cells. This has been a perennial problem of tumor cell substrates, or neoplastic cell substrates, or cell substrates for a long time, and, in fact, the issue has been out there and dealt with very effectively over the years, but each time the substrate changes some of the dynamics of residual DNA change and they require us to be back up and take a look at this situation again.

The consensus of the committee was that they agreed with panel one, that the risk of neoplastic activity with residual DNA for neoplastic cells is minimal to none, that there's really too little data on the possible infectivity of DNA containing whole viral genomes to assess the risks that might be posed by the presence of a latent virus genome or an infectious pro virus in residual DNA, were it to be present in sufficient length to encode for this type of process, and finally, there's no

evidence that human endogenous viral genomes are, in fact, infectious at this point in time.

We skipped over session five, because that was the Thursday evening session which I referred to earlier.

Session six, the task of section six was to review adventitious agent contamination, and the consensus that evolved from panel four, who was asked to discuss this topic, was that vaccines should not contain infectious agents, period, but adventitious agents do pose significant challenges to the use of neoplastic cells as vaccine substrates. Primary cells, again, represent – they were felt to represent a greater risk than neoplastic cells. The neoplastic cells posed risk for the presence of unrecognized oncogenic agents, such as endogenous retro viruses, herpes viruses, polyoma viruses and the new class of circo viruses.

The next consensus item was that needs to be a rigorous search for retro virus particles, and especially infectious retro virus in RT positive neoplastic cells. The presence of RV-like particles were not felt to represent – to be indicative of risk, but certainly their presence needs to be recognized, and a variety of detection techniques were discussed,

the complexities were such that I felt it wouldn't be appropriate to review them right now.

Then finally, and I think quite significantly, there was a considerable discussion about the possible presence of abnormal PrP genes, or the creation or the development of abnormal PrP genes in human neoplastic cells that needed to be addressed, although at this point in time there's no data that says abnormal PrP proteins that could be the product of such genes would, in fact, represent any threat.

The final session was asked to consider the development of designer cell substrates for vaccine manufacture, both the session and the panel, and the panel was asked to summarize the meeting.

The concept of designer cell substrates is one that involves using defined genetic elements, viral, oncogenes, cellular oncogenes, the induction of telomerase activity, irradiation and various other types of mutation events to produce a defined neoplastic event in normal cells. And, once you have that neoplastic event then that particular cell could be engineered to have to express various parameters of genetic activity that might be used to complement viruses or to simply be used to permit viruses to be expressed in cell lines that would be difficult to

obtain otherwise.

Under this type of situation, you would have maximum experimental control over the development of the cell itself, and this could, perhaps, have substantial advantages, since the material that you would start out with would be well known, well characterized, and in some cases it might have been used for vaccine production for many years. So, by introducing this proposal, which is now a very feasible approach to developing cell substrates, we hope to get a nice discussion of this process going, and, in fact, I think we did just that.

The consensus was that there are a wide variety of ways to effect immortalization of mammalian cells, and as I alluded to, engineering in this fashion allows step-by-step control of the process.

In spite of this, careful consideration – the panel felt that careful consideration needed to be given to what might go wrong, and then once the immortalized cells are developed they may pose issues like other types of neoplastic cells, for example, the creation of a PrP gene as a result of some abnormal mutation in the genome.

Finally, in summarizing the meeting, the panel considered that the defined risk approach that

I showed you earlier was a useful way to organize thinking about the process, however, I think the committee was a bit skeptical of our ability to generate useful numbers to address these levels of risk, and they thought that the outcome of this type of analysis would, at this stage of our knowledge, probably be suspect in some circumstances. However, I thought that they did think that when sufficient data were available to allow the application of this technique that useful information could be obtained.

And finally, that there was considerable discussion toward the end of the session on the risk posed by residual DNA and the fact that they are insufficient data, even though this question has been around now for probably 25 years, to dismiss it as a concern. And, I think the meeting ended on the note that it would be extremely useful for regulatory agencies, and CBER in the United States, and NIBSC, and, perhaps, the Paul-Ehrlich Institute and other institutes, regulatory institutes, to try to get together and develop a game plan, or a series of experimental approaches to answer this question, which most people think could be answered relatively simply once and for all.

I think that's sort of where we are. I'd

be happy to try to answer any questions. As I say, this was an extensive meeting, there was a huge amount of information presented. I think what we did accomplish, and we accomplished several things, at least from my superficial perspective, and the first thing was that as asked by the committee be got this information out before the scientific public. I think from the comments I heard the issues were favorably received by our colleagues, and I think they were quite enthusiastically discussed. And, I think that we also, at least from the folks that talked to me, there was considerable sympathy to the types of problems that we are trying to address here, and a number of people expressed a willingness to help us out in any way they possibly could.

CHAIR GREENBERG: Well, thank you, Andy, for reviewing what must have been an incredibly complicated meeting. I'm sure that many of you on the panel will look forward to receiving the documents which will be chock full of good science, actually.

We have time for some questions. We are, obviously, panel members, not going to be able to explore each one of those areas, despite many of your interests, but we do have time for some questions. So, if there are any for Andy.

Walt?

DOCTOR FAGGETT: Doctor Lewis, again, Walt Faggett. Thanks for a very clear, this is strictly very complex subject.

On the topic of genomic instability, you mentioned that there is a possibility of replication of some endogenous agents. What's the worst case scenario in that instance? What could that result in?

DOCTOR LEWIS: I think that, again, it would depend on the substrate itself, from my perspective, and Doctor Peden and a number of folks who were at the meeting are here, so I would ask a little help in this situation if I don't cover it completely.

In a human cell, I think that at least from my own personal perspective, the thing that I worry about the most would be the induction of a latent virus, and I'll give two for example. The first for example would be there's an increasing amount of data now accumulating on the presence of human polyoma viruses in various types of human tumors. I won't bother to mention them, but these viruses occur latently, and they are not too difficult to induce, and they are in most of us, and they are present in many of our tissues. So, I think the

possibility exists that this particular genome could, in fact, be induced to expressed as an infectious virus as a result of a mutational event within the cell itself.

Now, with this particular series of viruses we have some comfort, because we have the capacity to detect these agents with quantitative PCR assays at an extremely efficient level. So, I think it would be possible with this particular example to be sure that the genome was either there or not there before we ever developed the substrate. So, that's just one type of example.

Endogenous retro viruses in tissues other than man would, I think, present a possible problem, especially rodent and non-human primate tissues might be the source of endogenous retro viruses that could be activated by this type of technique.

And finally, the example of the PrP gene I think is the thing that gives us the most pause, because technology is not very good at detecting infectious PrP or prion activity at this point in time, and so, in fact, the suggestion was made by Doctor Cashman at the meeting that one way to deal with this would be the possibility of engineering a cell line in which the PrP gene was, in fact, ablated,

so that you could get rid of this problem once and for all.

CHAIR GREENBERG: Any other questions from panel members? No?

Well, if not, thank you, Andy, for moving ahead with this. I guess – can I just ask one thing? When will this circle back?

DOCTOR LEWIS: I was afraid you might ask that. Unfortunately, at this point in time, you know, we just haven't had a chance to digest this information, and, in fact, I was confronted just this morning when I was trying to put these slides together that the planning meeting for the next VRBPAC session meeting in November is tomorrow. And, I just think that it's not going to be possible for us to get this together for a week or two anyway.

Now, I would certainly hope that by the end of the month we should have a pretty good handle on what transpired at the meeting and what we gleaned from it and what we didn't glean from it, how it is going to impact on our immediate problems with dealing with some of the issues that are already before us, and maybe we can, in that period of time, we ought to have some idea of where we need to go in the future.

I would think realistically we should be

back before the committee in January. That would be my feeling. Doctor Egan may choose – and Doctor Patriarca may choose to set another agenda.

CHAIR GREENBERG: Well, that's always the case.

Thank you, Andy.

I'd like to move on now to our third update session, an update on RotaShield by Doctor Carbone.

Oh, and I am recused from conducting this session, so Doctor Daum?

For this one I'm allowed to stay in the room, for the next one I've got to leave.

DOCTOR DAUM: For the transcript record, I am Robert Daum, and I'm temporarily chairing this meeting for the Rotavirus item.

Doctor Carbone?

DOCTOR CARBONE: Thank you.

Today I'd like to review the chronology of the events prior to licensure and post-licensure of Rotavirus vaccines.

Just as background information, why are we interested in Rotavirus as an agent of illness in the United States? It's the single-most important etiological agent of severe diarrhea in infants and

young children worldwide. Virtually all children are infected by age three to five years, that's four out of five children, and notice that this is true of developed and undeveloped countries. Severe diarrheal disease is caused in children of three to 35 months, and in the U.S. it regularly causes seasonal diseases from November to May, depending on what part of the country you live in.

Specifically in the United States, the impact of the disease that causes half a million physician visits a year, that is one out of seven children, 50,000 of those children are hospitalized, that's one out of 78, and there are 20 deaths per year of children under five years of age, one out of 200,000.

Just as a little background about the agent itself, Rotavirus is an RNA virus and contains 11 segments of double stranded RNA as its genome. Because the genes are in individual segments of RNAase, you can actually end up with a chimeric or hybrid virus when two different viruses infect the same cell and the genes reassort. Therefore, progeny may have genes from two or more parent viruses.

There are many strains in multiple species, and there are multiple serotypes, and that

one single serotype, one single virus, is unlikely to be made into a vaccine, vaccines are likely to require multiple viruses. All of these issues with Rotavirus play a role in development of the vaccine itself.

RotaShield vaccine is the first licensed Rotavirus vaccine in the United States. It is a live attenuated reassortant of a rhesus Rotavirus, RRV strain, that contains a single human gene, the VP7 gene, for issues of immunogenicity. The vaccine itself contains four different serotypes, four separate viral strains, and was produced by Wyeth-Lederle Vaccines and Pediatrics. It was licensed in August of 1998, and recommended for universal immunization by these organizations.

The oral vaccine is used in children, it is administered orally and it's administered three doses at approximately two, four and six months of age.

I want to discuss some pre-licensure clinical studies. Prior to licensure, this reassortant was tested in studies that contained 15,000 participants. That includes vaccinees and placebos. However, there is no immune correlate of protection for this vaccine. What that means is, it's impossible to do a blood test, for example, to look at

an antibody level in any large-scale way and detect an effective response to the vaccine. Therefore, the effective response of the vaccine is tested by literally efficacy preventing or reducing the severity of the actual disease.

The efficacy with the licensed dosing against any kind of Rotavirus gastroenteritis is approximately 50 to 70 percent effective, against severe Rotavirus gastroenteritis it's approximately 70 to 90 percent effective.

The vaccine was licensed based on three major placebo controlled efficacy and safety studies, two performed in the United States and one in Finland. About 18,000 children received this vaccine at the licensed dose and formulation in these studies. However, we consider additional information from clinical studies that were performed in the United States, Venezuela, Brazil and Peru, and approximately 5,000 more children received vaccine in these studies.

A major concern, of course, with a vaccine which is a prophylactic treatment is safety. The problematic problem which concerns the safety of causal versus associated, and let me describe what I mean by that. In the label for this vaccine when licensed, were included adverse reactions. An adverse

reaction is something that is noticed both in the recipient of a vaccine and the placebo, but was statistically seen more often in vaccinees. Two examples were moderate fever and high fever were both seen more often in vaccinees versus placebo recipients in a statistical manner.

Then there's another category, which is also in the label for this vaccine, called adverse events. These are typically rare events, and in this case there was some gastroenteritis reported, meningitis, hepatitis seizures, intussusception, which we will focus more on later, failure to thrive and death. However, these are called adverse events because the rates are actual similar in vaccinees and placebos in the data, and, therefore, it's difficult to determine the causation or an association, versus an association with the vaccine.

Today we'd like to talk about a serious and rare adverse event associated with vaccination, and that is intussusception. First, let me discuss what intussusception is. Intussusception is a disease of the bowel where the bowel literally telescopes in on itself and can often lead to bowel obstruction. Signs of the disease include vomiting and bloody stools. It is typically identified by radiology

study, x-ray, sonogram or barium enema or enema of some sort, and it can be treatment by a non-surgical way, usually with an enema, or by surgery, actual surgery where the bowel is either reduced, the intussusception is reduced, or if the bowel has been damaged has to be recepted.

There are certain diseases which have been associated with the development of intussusception, including anatomical abnormalities, like Meckel's diverticulum, lymphomas, other congenital bowel diseases, infections, adenovirus, human herpes virus 6 and 7, Epstein-Barr virus, and even some bacteria strains have been associated with intussusception. Causality has always been difficult to prove.

Rates have been also difficult to prove in the general population of children, but generally it's been quoted looking at studies and reports from various health agencies of .074 to .05 percent in the first 12 months of life. That has been translated in other studies to suggest that we expect a reporting rate of 14 to 16 cases per week.

Peak age for intussusception in the general population of children is four to nine months, however, the range, as you can see here, is quite broad, from less than one month to almost two years.

Let's talk about the adverse events that were noted pre-licensure associated with Rotavirus vaccine use. Pre-licensure concerns are rare, but serious adverse events prompt analysis of data and a publication re intussusception. This is the publication to which that is referring to by Doctor Rennels, et. al. In this publication, you can see there's an extremely small number of cases of intussusception associated with the vaccine, and there was one case associated in placebo controls.

The rates were analyzed, and the rate in the vaccines of .05 percent was not statistically significant from the rate .022 percent.

I put this line here to prompt a discussion, issues of data analysis methods. As you can see here, it becomes very difficult because only two of these cases were in children receiving the license formulation, while three of these cases were in children receiving the other formulation. Some studies the children received one dose. Some studies they received three. Some studies they received 10^4, some studies 10^5 lots of virus. It makes it difficult to do comparisons among studies, and depending upon which studies you include, and, of course, including the appropriate placebo controls, the reanalysis of

the data has shown this number becomes .04 percent and this number becomes .03 percent, they move closer. So, it's a very difficult analysis to perform.

Of course, we are all concerned regarding any possible causality between intussusception and Rotavirus vaccine, and so the association requires further study. In pre-licensure studies, however, the RNAase distribution of vaccinees was similar to that seen in comparative unvaccinated populations. Wild type Rotavirus is not reliably associated with intussusception. There are several studies that have looked at this, the numbers are extremely small. Many of the studies have no control population to compare to, and the answers that they give are quite conflicting.

The lack of seasonality noted with wild type Rotavirus intussusception suggested that because wild type Rotavirus seizures was not followed or accompanied with large numbers of intussusception, or an increase or a peak, then that was believed to also provide more information that even wild type Rotavirus was not associated with intussusception.

However, because this is a serious adverse event, whether or not it's associated with the vaccine has to be looked into and continued to be studied.

Therefore, at licensure and post-licensure the FDA took action. Information regarding intussusception in the pre-licensure clinical trials was placed in the label for the public, for disclosure, for physicians and for patients.

A new VAERS term, that's vaccine adverse event reporting system, a new term for intussusception was added to the adverse event reporting system, so the reports from physicians and general population would be easily captured for review by the VAERS staff.

In addition, two post-marketing clinical trials were designed, and one, a very large one was specifically designed to capture serious adverse events and compare them to baseline population and intussusception was a major concern of our's when that study was designed.

The studies I referred to, one is 20,000 infants age six weeks to six months in an HMO system in California, and the computerized database allowed review of serious adverse events such as intussusception in a population of children who received the vaccine in the HMO and a population who did not.

Study two, which was not initiated because

of the recent events, was planned to study age-specific adverse events following vaccination at older ages than currently recommended in the license and younger ages of children, to look at age-associated adverse events.

So, what did these studies and other information reveal to us? Post-licensure data that were obtained, after an estimated 1.5 million doses were administered between licensure and June of 1999, revealed that in VAERS reports of 15 cases between September 1st and July 7, 1999. What was concerning was that this reporting rate was approximately the same rate as seen in the population, since this is a passive reporting system, we anticipated lower than normal rate of reporting. So, this prompted concern.

Secondly, the post-marketing clinical trial between December and June, pardon the typo, please correct this on your handout, nine total cases of intussusception were reported in the large post-marketing clinical trial in the HMO, three of them were in vaccinees.

An MMWR analysis, you see the citation down here, indicated a possible trend of association with intussusception, although it was not statistically significant there was concern because of

an increased risk in the first and second week after the first vaccination and a change in the typical age of intussusception was somewhat earlier in infancy following vaccination.

Actions taken, on 7/15/99 the CDC made a recommendation of cessation of vaccination and initiated a case control study. After consultation with the FDA, the manufacturer notified the vaccine purchasers via telephone of this information, hand delivered a Dear Doctor letter to cease vaccination pending further data collection. You can see that happened fairly prompted. In addition, fairly promptly, the manufacturer went with personal visits to the purchasers and places do not use stickers on remaining vaccine inventory in the purchaser's supplies.

A multi-center research group was initiated, with participation by government entities, NIH, CDC and FDA, universities and industry. The major concerns of this multi-center group are the fact that there is some disagreement and a large amount of unknown information about what exactly causes this intussusception. There are some theories about physical issues and mechanical issues, but the actual pathogenesis and mechanisms really are not known.

And then, of course, the major issue of, is Rotavirus vaccination associated with an increased risk of intussusception? This group is addressing this in a clinical epidemiology standpoint, of course, the CDC case control study qualifies there, pathology of the children affected and if there are any surgical materials available to evaluate that. And, of course, basic scientists gather to discuss pathogenesis, a mechanism to further evaluate this problem.

Just a little information about the CDC studies that have been initiated. There is a case control study headed by Doctor Warden. At this point, the study has 400 enrollees, that does not mean 400 people with vaccine-associated intussusception, I wanted to make that clear, that's simply children enrolled in this study, a one to four case ratio to controls. Enrollment will end late October, and then the data will be analyzed, and, of course, it's not appropriate to present or analyze the data prior to finishing the enrollment, so that will come later.

A cohort study has been initiated by Doctor Chen's group, based on several medical care sites, and a retrospective review of another large database similar to VAERS, vaccine safety datalink, to detect whether other vaccines or other diarrheas may

also be associated intussusception, also by Doctor Chen.

The case control study that was mentioned, which will end in October, gathers information on all cases of intussusception, and focusing on states with the highest distribution of Rotavirus vaccine. That's simply to get enough numbers to provide a meaningful study.

The study includes all cases with radiographic or surgical confirmation diagnosed between these dates in children age one to 11 months. There are age match controls with no intussusception selected from infants at the same hospital as the cases, and the comparison will be of expected intussusception rates based on the placebo subjects and changes in these rates, if any, seen in vaccinees.

So, in summary, Rotavirus causes significant disease in the United States and tremendous death internationally in infants. There has been licensure of a new Rotavirus vaccine. There have been administered over a million doses, and they were associated with a rare but serious adverse event intussusception, and the data are insufficient at this point to decide whether there's causal association.

CDC, FDA and other groups are pursuing

additional clinical, epidemiological, and scientific data to determine if association is causal, and further regulatory actions will be taken pending review of this new information.

Thank you.

DOCTOR DAUM: We continue to do well in terms of scheduling, so we have time to discuss Doctor Carbone's presentation or ask questions of her.

Doctor Ferrieri?

DOCTOR FERRIERI: My question is whether we know anything about pathology within the abdomen at surgery in those infants who underwent surgical correction of the intussusception, were there other abnormalities found? For example, lymph node enlargement, anyone with an associated other abnormality or congenital defect.

DOCTOR CARBONE: That issue is actually being studied. That's part of the multi-center group and the pathological assessment. It's difficult to give any numbers or significant data because it simply has not been studied. We receive reports post-fact, and surgical reports after the fact.

However, some surgical reports that we have have noted some lymphadenopathy, enlargement of the lymph nodes, and some have noted some death to the

bowel, it's intussuscepted, of course, the blood supply is cut off if it's a long enough time.

But, as far as detection of other pathogens, there's been no organized search because these are clinical cases. In the retrospect, the pathological group is going to be evaluating exactly that.

DOCTOR DAUM: Ms. Fisher, I think you were next.

MS. FISHER: It's my understanding that there have been 100 cases of intussusception following Rotavirus vaccine reported to VAERS and two deaths. Is that correct?

DOCTOR CARBONE: As of September 9, 1999, there were 99 cases reported to VAERS, people reporting intussusception in children who had received vaccine. In addition, there have been two deaths reported in children who have received vaccine, who later – one of those cases – let me say, those cases are currently under review, there's some information on one of those cases that the infant may not have had intussusception at all based on pathology reports, but that's very preliminary information, and those cases require – are currently getting further review.

MS. FISHER: I have one more question –

DOCTOR CARBONE: Excuse me, VAERS is a passive reporting system, and the first 15 cases that were reported were reported completely passively. Those arrived at the FDA with no prompting. All subsequent cases, and there's been an enormous bump, have been reported following publication and announcement by the CDC. That we can really not consider passive reporting any longer. So, the increase in rate following the CDC report may simply be an increased awareness in the public, and we consider those reports very seriously. It's not like we dismiss them. However, in terms of numbers, the change pre and post that day are a difference between passive and more active reporting.

I just wanted to make that clarification.

DOCTOR DAUM: Do you want a follow-up question?

MS. FISHER: One follow-up. In the original licensing studies for this vaccine, what was the length of follow up, what was the follow-up period to look for such things as intussusception?

DOCTOR CARBONE: Good question. The studies, of course, are numerous and varied. Length of follow up were usually no less than 42 days following vaccination, and in some cases were up many

months beyond that. In some cases, the studies went for two seasons, so the children were actually followed for over a year.

DOCTOR DAUM: Doctor Adimora?

DOCTOR ADIMORA: I may have missed this in your presentation, but to what extent was RotaShield marketed and distributed internationally?

DOCTOR CARBONE: Well, I'm U.S. FDA, so it's licensed I the United States and we follow the U.S. distribution. I don't know if anybody would care to comment on international distributions.

DOCTOR DAUM: Is there someone in the audience, Peter, who would like to comment? Come up to the microphone and identify yourself.

EXECUTIVE SECRETARY CHERRY: Please use the microphone.

DOCTOR DAUM: Can you talk to the microphone and tell us who you are?

MR. RUSSO: I'm Carlo Russo from Merck. RotaShield was approved in Europe in May, so it was licensed in Europe.

DOCTOR DAUM: Has it been used?

MR. RUSSO: That I don't know.

MR. PARADISO: Thank you, Peter Paradiso. It was licensed in Europe. It has not been

distributed or used anywhere outside the United States to date.

DOCTOR DAUM: Thank you for clarifying that.

Other comments? Doctor Faggett?

DOCTOR FAGGETT: Yes. The 99 case, what was the average there of incidence, and also, you mentioned, what, four to six as the average age, I'm used to the age being a little older. That's a two-part question.

DOCTOR CARBONE: Those data are difficult to come by, and let me explain. In various data, because they are reported to us, there is no control over possible selection biases, so these data can be analyzed, but as to what they mean we don't know.

It turns out there's only about a month or a month and a half difference in age, with the children in the various databases. Preliminary analysis, let me emphasize, may be slightly younger than the average age quoted for the population, but as you've noted, even finding out what the average age for the population is is very, very difficult to know.

The concern was possibly most stimulated by the fact that in the reported cases the vaccination occurred, had occurred in most of these cases about a

week prior to the report. Of course, there's also the bias that anything that happens in closer association to vaccination is likely to be associated with the vaccine, even if it's a random event.

So, I apologize for not being able to give you the exact data, but they really aren't available even for the normal population.

DOCTOR DAUM: Doctor Karzon, please.

DOCTOR KARZON: The pathogenesis of this illness is not fully understood. Is there anyone looking at the microbial flora in known cases that are diagnosed?

DOCTOR CARBONE: There may be investigators out in the scientific community looking at that, but from our point of view Doctor Breiman's group, the multi-center working group, that's one of the approaches that's going to be taken, to review the cases and look for associated – for example, there is a report in the literature in children where they've looked for Rotavirus in children's intussusception and actually found adenovirus also present in the majority of those children, as well as adenovirus present in children who have intussusception and no Rotavirus present.

So, that is absolutely a very important

question, and that will be addressed.

DOCTOR DAUM: Doctor Snider, then Doctor Kim.

DOCTOR SNIDER: Dixie Snider, CDC.

I just wanted to point out to everyone that this case control study is a massive undertaking. It requires hundreds of people. It's consuming time of most people in the National Immunization Program, and, thank goodness for all the people that CDC has stationed in the States, and for all the state health departments and other health care provider organizations that are helping out with this investigation.

I know it sounds like a long time to the end of October before we finish up this study, but it is a massive job trying to track down all these cases, and then the four controls per case to get the information that's needed.

So, I just wanted people to be aware that lots of effort is being put into this, lots of resources, to try to get the answers as quickly as we possibly can.

DOCTOR DAUM: Kwang Sik.

DOCTOR KIM: Doctor Kim from Los Angeles.

My question was partially answered by

Doctor Snider, however, just looking into the numbers that you presented, rate of intussusception was about one per 10,000 before licensure, you know, in your document, which means that if you immunize 1.5 million than you anticipate about 15 cases. So, the question comes up, is that what is the interpretation before licensure, which is one per 10,000 versus, you know, after licensure, which is 15 per 1.5 million, what is the – what made your interpretation somewhat different, I guess, in terms of looking for numbers?

DOCTOR CARBONE: Let me rephrase that to make sure I understand. What you are saying is the rate after licensure isn't very much different from the rate prior?

DOCTOR KIM: No, it's the same.

DOCTOR CARBONE: Right, it's the same from the rate prior, and, therefore, why were we concerned.

One of the reasons we are concerned was because the information – we feel that in many ways we appropriately stimulated a public concern about many of the adverse events of this vaccine to the label, that's normal, you put in the label adverse events. Physicians read that and, hopefully, patients have access to this information as well.

Therefore, one concern is that when people

find an adverse event following a new vaccine it gets reported at a very high rate. However, we still assume that because of the passive reporting system, as few as five percent or ten percent of the cases will actually be reported. Therefore, when we see a rate in a passive reporting system that equals the expected rate, we become concerned and investigate that.

Did I answer your question?

DOCTOR KIM: Yes.

DOCTOR CARBONE: Thank you.

DOCTOR DAUM: I actually have a question.

I'm very impressed at the response that the entire vaccine community has made to this issue, the speed with which everyone from CDC, to FDA, to manufacturer, responded by picking this up and acting, and I'd like to know whether you think there's any precedent for responding at this kind of speed, and whether this is — I think it's something that everybody should sort of take a bow for and really feel good about how the system appears to be working. I wonder if you'd like to comment on that.

DOCTOR CARBONE: The only thing I'd like to say is that I think it just reflects the concern that we have in doing the regulation and putting out a safe

and effective product. And, it simply was what we felt the right thing to do.

DOCTOR DAUM: How will you address, let's say that the case – let's take the worst case, and the case control studies establishes causality, how will FDA, or other agencies for that matter in your opinion, view testing of future Rotavirus vaccines with respect to rare side effects?

DOCTOR CARBONE: I think that's a terribly sticky wicket problem. Obviously, that's a $64,000.00 question, and I think that one of the big problems we are dealing in this is this massive, vast lack of information, even about intussusception as a disease itself. And, I think it makes sense that if we find out what causes intussusception, or at least get a handle on some mechanism, what the relationship between infectious agents are and intussusception, that, perhaps, a vaccine could be designed to specifically avoid the problems.

But, it is a vast ranging problem, including even oral delivery of vaccines at all, if there's other association.

I can't really make any specific comments about plans, not knowing what we are going to find down the road, except we are considering the

possibility from all directions, in our laboratory we actually have a very talented young scientist, Doctor Atreya, who of his own volition developed a Rotavirus lab to start looking at adverse events about a year and a half ago when we were investigating the vaccine, and he's made some good headway. There are many people, obviously, at the CDC, Doctor Snider was talking about the effort, and in the larger community, so because this problem has finally risen to the surface, and we have many different ways to investigate it, I think that – I actually am very hopeful that a mechanism will be found and a way to protect children against Rotaviral diseases will come around. It's not particularly obvious right now because we don't have enough information.

DOCTOR DAUM: Doctor Estes.

DOCTOR ESTES: I think many people have raised the question about whether this has been a problem with the live oral polio vaccine, which is probably the oral vaccine that we have the most experience with. And, can you comment on that, or at least let us know what's being done to look at that?

DOCTOR CARBONE: That's actually being looked at very intensively. The data on this are very, very preliminary. The polio in the intestine

causes a very different type reaction and a very different location of reaction than Rotavirus does. However, there is some hints in careful, careful study that there are a few cases that may have been associated with polio virus vaccine, but it's very preliminary, I stress association rather than causal, but there are several groups that are looking very intensively at that and other orally-delivered vaccines.

DOCTOR DAUM: If there are no other questions, I'll just make one final comment, and that is that outside of the United States in developing countries this disease is an even greater impacter on pediatric ill health than it is in our country, and it would be crucial to clarify this issue so that we can deliver the vaccine to children in developing countries once the safety issue is clarified.

And, with that, I will step down and turn the floor back to our erstwhile Chair.

CHAIR GREENBERG: Thank you.

And now, we will move into Session 4, which is a briefing on selected individual research programs, and for an introduction we have Doctor Thomas Hoffman.

Doctor Hoffman, this session moves along

reasonably quickly, so –

DOCTOR HOFFMAN: My name is Thomas Hoffman. I'm the Acting Director of the Division of Allergenic Products and Parasitology.

I'm going to depart slightly and introduce each of the two presenters in turn, rather than introduce both at this time as it is on the program.

The first person that you'll hear from is Doctor Richard Kenney. Doctor Richard Kenney, Rick Kenney, came to CBER as a Senior Research Investigator in 1995, after completing a fellowship in infectious disease at NIH, and taking further training in parasitology at the NIAID LPD.

The major thrust of his laboratory work has been on the immunobiology of and vaccine development for Leishmaniasis. His projects focus on human Leishmaniasis, a protozoan parasitic infection of the skin or visceral organs that is transmitted by sand flies. His lab uses a variety of techniques to pursue research, including molecular biology, cell and tissue culture, cytokine analysis and pre-clinical studies in mice and monkeys, as well as human clinical studies in patients will visceral or cutaneous disease, their families and in volunteers.

Thirty to 50 percent of Doctor Kenney's

time is spent performing regulatory functions, which includes the clinical review of parasitic vaccines and related products. This work involves extensive pre-submittal support, review of IND submissions and amendments, training in all phases of review, statistics, clinical trial design and clinical activities.

Doctor Kenney also supports regulatory projects involving DNA vaccination, allergenics, micro bacterial INDs and the International Committee on Harmonization Policy Development, as well as preparation of guidance documents. He serves on several external committees for both malaria and Leishmania research.

Doctor Kenney maintains collaborative projects in India and Brazil. Doctor Kenney also retains a close collaboration with the Laboratory of Parasitic Diseases at NIH, where he holds a dual appointment.

He is an attending in the Infectious Disease Consult Service at NIH, and is an active member of the Tropical Medicine Consult Service.

Doctor Kenney will describe his current research projects and collaborations in a moment. Doctor Kenney has received a number of important

awards and peer recognition. He and his group received the Sigma Chi award for their vaccine trials in primates at the annual FDA's Scientific Forum in 1997. Doctor Kenney was the principal investigator for an employee invention report that was submitted and accepted in January, 1998, for development of a vaccine that contained heat killed Leishmania, and recombinant human IL12 and alum as adjuvants. In May of 1998, Doctor Kenney was awarded the PHS Outstanding Service Medal in recognition of his outstanding accomplishments in the field of Leishmaniasis in India.

Doctor Kenney has made important discoveries in his chosen field, as you will hear. He has made vital contributions to the regulatory programs of the division, as a basic scientist and clinical reviewer. In addition, he has made an important impact on global public health through his international activities.

On a personal note, although I do not supervise him directly, Doctor Nakhasi, one of our lab chiefs, does, and I have always found Rick to be energetic, good natured and even tempered. He takes on a multitude of tasks that would ordinarily be considered to lie outside of his job description. He

is a remarkable clinician whose work is consummate and enviable, and who adds important depth in this area to the Office of Vaccines.

Rick?

DOCTOR KENNEY: Thank you very much, Doctor Hoffman, Doctor Greenberg.

They have asked me to give a very brief overview of some of the activities of our lab, to try to show you folks what we are trying to do.

If I could have the first slide. Maybe, maybe not. This will be a short talk if we don't have slides.

Leishmaniasis is not a typical disease that people have heard of, although it even affects people down in southern Texas. It's a worldwide infection, it's been a scourge in the world for many centuries. It is one of the top five parasitic diseases that the WHO targets the vaccine development, and, thus, is an important infection for our lab and for the FDA as a whole, we believe.

The disease comes in two flavors. There's cutaneous disease, or a skin disease, where an ulceration forms at the site of the bite of a sand fly. The protozoan parasite is able to go into the site, infect macrophage, and you develop a chronic

infection, a chronic ulceration that lasts somewhere between four months up to two years, and occasionally produces other complications. This type of a disease occurs endemically, happens all the time in many regions throughout the tropics.

The other type of disease is called visceral Leishmaniasis. This is an inflammation of the spleen and the liver, where you get dramatic enlargement. It's generally fatal over the course of about eight months without proper treatment. This happens epidemically, usually focuses in Brazil, in The Sudan where it kills more people than their recurrent civil wars, and in eastern India.

Next slide, please? Do I have the gadget? Oh, great. Okay. There we go.

I'm a clinician, we parasitologists have to show one gross picture at least. The disease worldwide causes a lot of morbidity, more than mortality. The infection, though, can be scarring, and is generally socially unacceptable and, thus, is a focus for vaccine development to try to alleviate most of this morbidity.

This infection has lasted for several months and will probably last for several months more. It will self cure. The goal of the vaccination, of

course, is to avoid this type of occurrence.

It was noticed about 100 years ago that you could vaccinate with a live organism. Unfortunately, that vaccination also has its own adverse events and was dropped about 20 years ago.

Over the past time since, there have been many labs that have been trying to produce vaccines that are from killed antigen. Basic concepts of vaccine development are like building blocks, they are all based on basic immunology. The way to get to a final vaccine is to choose the right antigen. These have to be tested in preclinical studies and go through clinical trials to prove that they are broad utility.

The program that I've tried to develop over the past four years has focuses both on the basic immunology and on the eventual development of a vaccine that might be useful for Leishmaniasis. This is the only hard slide. The focus that we've done in our lab here has been on phosphorylation of the interferon gamma receptor. The general concept for the activation of macrophage, which is the cell that Leishmania infect, is that there are several pathways. The one that we've focused on is the signaling by interferon gamma, a cytokine that transmits signals

between cells. When interferon gamma comes and attaches to the receptor the alpha and beta subunits are the site of attachment, the alpha receptor becomes phosphorylated by Janus kinases that are present in the cytoplasm. These kinases themselves become phosphorylated and transphosphorylate another cytoplasmic factor called stat-1.

This is the signal transduction pathway that gets the gamma interferon signal down to the nucleus, where it stimulates the production of messenger RNAs and proteins to activate the macrophage. When Leishmania invade a macrophage they inhibit many pathways, one of which is that they are known to inhibit the phosphorylation of both the stat and the jak kinases.

Unfortunately, the mechanism for that hasn't been known. What we did was to take antibodies and look at the receptor, the surface receptor itself, and surprisingly found that Leishmania somehow caused the direct down regulation of production of the alpha subunit of the receptor, so there's no alpha subunit when gamma interferon runs around, that cannot transmit a signal and you don't get activation of the macrophage and the macrophage is unable to kill the Leishmania.

In terms of the vaccine development, the main cell that is used for immunogenicity against Leishmania is the T-cell. It's a cellular disease, it's much more than antibodies. T-cells differentiate into two flavors. One is the T helper 1 type cell, which in terms of Leishmaniasis is a good T-cell. It produces interferon gamma and IL-2 in response to differentiation by interleukin-12. Interleukin 12 is the cytokine that is produced in K cells and other cells and in monocytes, that causes this differentiation pathway. Other T-cells can differentiate to Th2 cells in the presence of interleukin-4 to produce more interleukin 4, 5 and interleukin-10.

In-bred strains of mice are either susceptible or resistant to Leishmaniasis based on the development of Th2 cells or TH1 cells. The mice that die, the susceptible mice, have been found to have an increased amount of IL-4. The resistant mice have an increased amount of IL-12. It was found about four years ago in Phil Scott's lab in Philadelphia that if you give interleukin-12 with antigen you can vaccinate a susceptible mouse and make it resistant, and this is the basis for the current effort in vaccine development. So, if you give IL-12 with antigen, you

get a lot of T-cells, Th1 type cells that are producing interferon gamma.

We spent a fair amount of time in various mice studies trying to determine which antigen must be the best for a vaccine, and we compared native, autoclaved, protease inhibitors. We aged it a little bit and autoclaved it, we filtered it, basically we found that if you autoclave an antigen it works as well or better than the native crude antigen in this vaccine.

At this point, the field is not to the point where we have a recombinant vaccine. There's a lot of different antigens that look hopeful, but we are still not at a point where we can choose a single recombinant antigen. So, the whole field is using crude antigens.

We took this autoclaved antigen, we are calling it heat killed Leishmania vaccine, into a couple of monkey trials to show the safety and immunogenicity, comparing antigen alone with adjuvants alum, or aluminum hydroxide, and this interleukin-12 that causes Th1 cell development. We did a dose escalation using 40 nanograms to 100 nanograms and one microgram in various groups of monkeys along with antigen and alum, to give a dose escalation that's met

on IL-12. We also did a study where we looked at decreasing doses of antigen, I don't know if that can be focused any more, thanks, where we had one milligram, half a milligram, and .25 milligrams of antigen to try to minimize any side effects. Twenty-four monkeys were in each experiment. These were vaccinated once. This is Curious George. They were vaccinated in the arm, my little prop here, subcutaneously. We tested for safety in immunogenicity, we found that there was adequate immunogenicity and interferon gamma did appear in the presence of antigen in cells that came out. And finally, we used the monkeys in a challenged model, where we infected in their forehead, and several months later followed the course of this infection. The monkeys serve as a useful way to see whether or not the vaccine works. They developed a fairly typical lesion that is quite like the human lesion.

So, just one data slide here, this is a little hard to see again, the antigen, if you vaccinate with antigen alone, and then infect one month later and follow the size of the lesion, this is the maximum lesion size with antigen alone, compared to saline alone. It's been known in mice that antigen causes larger lesions than saline. This antigen is

being used in vaccine trials throughout the world. Unfortunately, nobody has really looked to see whether it causes worse diseases because we don't have a challenged model in humans. Nonetheless, if you combine the antigen with increasing doses of interleukin-12 the lesion that develops after infection, after challenge, is smaller. So, for the first study we were able to show that there was a dose response to IL-12. In the second study, we decided to go ahead and use two micrograms of human IL-12, in combination with the antigen at various doses, and, in fact, were able to protect 12 out of 12 monkeys. None of these 12 monkeys developed lesions if they were given the combination of the three agents, versus all four of the saline controls, if you leave out either antigen, either adjuvant, excuse me, we had one of four monkeys in each group develop a lesion. And so, we feel that the most effective vaccine is probably going to be something that combines antigen, alum and something like interleukin-12. The safety and immunogenicity, like I said, were established. We are using this data as the basis for a human trial.

The further monkey trials we do will compare this successful vaccine in the monkey challenged model with oligo nucleotides, short pieces

of DNA that have the special capacity, they are called CPG oligos, to stimulate Th1, stimulate this interferon gamma response, versus a true DNA vaccine where we have inserts of various antigens on a CPG Plasmid backbone.

Finally, the human trial that we are about to start compares antigen with the combination of antigen and alum, low doses of IL-12 to begin with, and a dose escalation up to what we feel would be an effective dose and, of course, a safe dose in various groups of humans. This will be done at NIAID staggering each group to increase safety.

So, in summary, lab works, clinical studies, both here and in Brazil and India, though I didn't have time to show you those, we've spent a lot of time searching for different potential antigens. We've done these three pre-clinical studies in mice and monkeys, and we're at the stage now we are moving into humans and planning to do future studies at sites that we are collaborating with in Brazil.

Thank you.

CHAIR GREENBERG: Thank you, Doctor Kenney, for that interesting talk to buff us all up on Leishmaniasis.

Doctor Hoffman, are you here for your next

introduction? I'm not going to have any questions, because I'd like to move along.

DOCTOR HOFFMAN: Our second talk will be by Richard Pastor. Doctor Pastor is Chief of the Laboratory of Biophysics in the Division of Allergenic Products and Parasitology, a position he has held since 1996.

His laboratory characterizes components in vaccines and allergenic extracts, including adjuvants in delivery systems, using biophysical methods. His related regulatory responsibilities include lot release of vaccines using NMR and light scattering, and review of INDs and PLAs for adjuvants, grass extracts and LAL test kits with an emphasis on their physical chemistry.

Doctor Pastor's specialty is computational biophysics, and he frequently addresses general mathematical and computer science issues faced by CBER, such as statistics of lot release and stability protocols and modeling of adverse reactions.

Doctor Pastor will describe his current research activities in a moment.

Rich's science will speak for itself, so I wish to touch on his role as a mentor and manager within the division. Without doubt, he is a leader

among the lab chiefs, who is able to mobilize his peers to analyze the goals and direction of the division and to take effective action in executing them. He sees problems and solutions that are often obscure to others, and he has devised ways to implement agreements that all involved can see as in their interest.

Rich is, above all, a teacher and mentor to his staff and other junior members of the division. He sacrifices his own time and energy to see to it that their personal or resource needs are met. His peers recognize Rich as an outstanding resource for scientific discussion.

In 1997, he was acknowledged by the agency for outstanding achievement for excellence in science by a group. In many ways, he is a throw back to the scientist who spends most of his time thinking, discussing and arguing science above all else.

Doctor Pastor continues to make remarkable strides in his chosen field of research, while simultaneously supervising and mentoring young students and investigators in the art and science of research. He has evolved into one of the most experienced, capable and innovative administrators and managers in CBER.

At his site visit, I surprised and embarrassed him with a comparison to Martin Arrowsmith from Sinclear Lewis' Pulitzer Prize winning novel. I feel so strongly about the aptness of what follows that I'm going to repeat the description of the protagonist in that novel that applies readily to him. "Martin had one characteristic without which there can be no science, a wide-ranging sniffing, snuffling, undignified, un-self-dramatizing curiosity, a curiosity where he saw nothing as ordinary and it drove him on."

CHAIR GREENBERG: Doctor Pastor.

DOCTOR PASTOR: Thanks.

So, I'd just like to give an overview and some broad brush strokes. So, in my first slide I'll just give you an overview of the biophysics lab. The second one, just a comment on the sort of modeling we do. It's interesting, it's like new, it has its problems. And then, in the three next slides I'll give you one slide each on my areas of research and then where I'm trying to go with each one of them.

The biophysics lab, as you have in your handout, and it's on the web site, I believe, this is just an overview of the three areas in which we work in the biophysics laboratory. One is NMR

spectroscopy, one is a simulation, and the other one is light scattering.

If you were to spend some time on this slide, you'd see that each area has a certain problem to it, it solves certain problems, it like has other problems, and what we're trying to do in the lab, to the best we can, is to work on projects in which these areas compliment each other, and as a group we can get a better understanding of biopolymers and vaccines especially.

My area is modeling. It's a computer simulation method, but it's basically solving just the equations of motion of the system, four – mass – acceleration, essentially. You put the system on a computer, on a super computer usually, you run it for a month or two, or sometimes even six months. Out of that comes a path, and from that path you'll gradually get a structure that the system wants to be in.

Some examples of that, at least ideally, would be a structure of a membrane complex, so you're lipids are here, you have a protein here, and say you have a drug binding here. If you didn't know where the drug bound, or how the lipids rearrange itself in the membrane, in the future one could just put all these things into your system and just run it. It's

a pretty amazing idea.

Another sort of structure would be if say you have a polysaccharide vaccine, or a protein vaccine, you add an adjuvant to it, say some kind of surfactant, you could literally put that all in a big computer, you know, system, run it and see what the structures of that thing are, where the adjuvant binds, how it changes the structure, ultimately how it will interact with the cell itself.

So, it's a method that just has fantastic promise, and I can guarantee that eventually this is how we are going to do a large part of our science.

Now, why can't we do it right now? Basically, our computers aren't fast enough. That means that we can't do quantum mechanics. Sometimes we have a chemical reaction, you have to have the quantum mechanics. We can't really do that yet. Our force fields are not exact, many details about that, other than to say that, you know, we do a pretty good job on order, but we don't get it perfect. So, it's an advanced area. And, because we are solving equations, you say, well, how long can you run this thing for, well, basically, we can run them for on the order of 20 nanoseconds, that's 10^{-8} seconds, we might want to run something that would take as long as a

minute. Well, that's a factor of 100 million there you need. But, we will get there.

So, there's sort of a bottom line to this, is that we can do a lot, we can't do everything, and you have to choose your problems very carefully.

So, the first problem I'll talk about is sort of this one, and so what have we done? Well, I'm going to to take all of this stuff out, and in my area that I've been working on for many years is lipid bilayers, and I don't have a nice monkey to show you, but I do have a nice bilayer. And, as you see, a lot of the – this is now in like textbooks, if you generally see the picture, that's one of mine, and we've learned a lot from this bilayer. This is just a snapshot from a simulation, but basically you can see that the lipids are somewhat random, they are hanging down, but they are not hanging straight down. They are extremely fluid. Water binds to the surface in very interesting and important ways, and if one were to follow a small drug molecule going through that thing you could see it go through.

Where does this go eventually? Well, a bilayer, this is just a little snapshot, of course, of a liposome, so and one of the things we are interested in vaccines is like doing vaccine delivery through the

liposome. Ultimately, we could in a simulation put the vaccine in that liposome, adjust the lipids that you actually want and run that thing, see which lipids are better.

The other little area I just want to touch on is just the early results we have on simulations of a micelle. We've simulated octyl glucoside micelles by themselves, and now we are at the stage where we are putting a peptide in. I only want to make one point from this picture, if you pull the peptide out, just graphically, you can see that effectively the peptide is in, essentially, a cleft of all the octyl chains, so it's fitting in a pocket in this micelle, thereby making it more stable. Ultimately, we hope to use this kind of system to understand the interaction of vaccine adjuvant complexes.

That's a little slide of another kind of modeling I do. This is an oligo saccharide. In this pentamer, the experimentalist has a problem that they couldn't – they did NMR on it, and they couldn't separate the effects of what they were seeing. There was a possibility that you were getting this odd pattern of spin lattice relaxation times, because the molecule was kind of a cylinder, but was it because it was rotating as a rigid cylinder or was it

isomerizing, or just in a sense wobbling a lot at the very end. You might say why is that important? Well, the flexibility and confirmation of these polysaccharides is important to understand. This is our way into it.

We then applied three different techniques to it, all of which I actually, you know, kind of worked on, sort of invented. So, basically, we fit the NMR using an anisotropic model which we originally published in '95. We did a modeling, which we also did in the lab, to actually get what the shape of this polymer was, and then I did a kind of simulation called Langevin dynamics, which I published a lot of work on.

By doing all of these three, not just one, and certainly not just none, we were able to separate the effects and prove really very conclusively that, in fact, the entire effect was just due to a libration of that last ring. So, in other words, the thing is actually pretty rigid, but it just has a floppy tail, but we were able to, like, pin that down precisely.

This is in present JACS. What is the long-range goal of this? Well, as we understand these little pieces of polysaccharides we can understand much like longer polysaccharides. The point is,

really, you have to understand them well.

The second to last slide, on allergenic extracts. I was the Acting Chief of the Allergy lab for about a year, and one of the issues we really had to face was, how do you lot release well? The problem of allergenic extracts is that there's a huge variability in both the extracts, the tests are biological tests with a large variability, and the people are also quite variable. The allergic response varies tremendously between individuals and even the same person on different days.

So, therefore, we really had to face very directly that one needs to balance what you call the manufacturer's risk in any lot release situation, and this manufacturer's risk is that because of the variability of the tests you sometimes have to throw out a perfectly good lot of vaccine. In other words, if they submit the reference themselves, sometimes you are going to have to say, sorry, that fails, that's the natures of the testing.

Likewise, you are going to have to say, well, what if something is right on the edge, you want to catch that most of the time, can you catch it all the time? No. If you never make a mistake, you'll never pass a single lot, you'll throw out everything

because you want to be too careful to some extent.

So, what was the problem we specifically had to face? One was, what are the limits of these relative potencies for an ELISA assay for these two kinds of extracts? They were set previously, we wanted to look at them again, so we basically – and what's the specific problem, if you are getting allergen therapy after the bottle expires if you want to switch manufacturers they have to give you a new bottle, what kind of a dose change are you able to like get and not keel over, or have an adverse reaction?

So, what we did there, we did a really combined study that's pretty interesting. We haven't paid for this, it's been like submitted on it, where we look at the dose response, it hadn't really been done before but we did it, and we found that a factor of four, interestingly enough, leads to a five percent increase in adverse reactions.

Then, we went and checked by looking at the observed values of like all the lots of vaccines that like CBER had like gotten in the last several years, and then worked backwards, to make a long story short, and to see what is the distribution of like this – of the manufactured lots. And, in fact, it's

really quite tight, much tighter than we really expected.

Because of this, we can actually, we are in the process of widening the limits slightly, but only widening it after a very careful analysis that we are well within that factor of our. So, I'm kind of excited that we were able to do — to solve a problem in a way that could actually lower the manufacturer's risk without impinging on a consumer's risk at all, it's quite low. That's an ideal, I think.

Long-term goals, we can do this for everything, now that we really have a thought process worked out.

My next slide is where I want to go. This is basically a whole series of like areas and like membranes. We are almost finished with the simple lipid bilayer, and now we want to start to add peptides to it, work out what the real — where the lowest free energy state, make the lipids more complex. We want to continue working in like sugars. In fact, we are starting to work on an interesting project of like toxins with self-surface, like gangliosides. I'm not done with the allergy work, I'm still working with my pals there, and we, you know, are going to finish that up soon.

Long term, back to the big picture, on the Star Trek picture of the thing, we'd like to simulate a whole patch of like membrane, just do it. Likewise, we'd like to simulate a huge complex with vaccine and just an adjuvant. All these things are well within our, you know, ten years or so we'll maybe be there, and likewise, as I said in the last slide, look at some of the limits for these other vaccines regulated by OVRR.

Thank you very much.

CHAIR GREENBERG: Thank you, Doctor Pastor, and in the interest of time there won't be any questions from the committee, but thank you very much.

We are now going to move on to the session that you all love, the open public hearing piece, and at this point I ask the audience whether there's anybody that wishes to address the committee.

I'm told that there is one person that has identified themselves previously, Doctor Michael Young, the Chief Science Office from Medeva, is that correct? Okay. And, I'm told that you need about five minutes, Doctor? Okey-dokey.

DOCTOR YOUNG: Good afternoon.

As the Chief Scientific Officer of Medeva, the UK's largest vaccine manufacturing company in

worldwide vaccine research since our acquisition of the Wellcome vaccine products and R&D in that area, I feel it's appropriate for the committee to at least hear something from an industry perspective going back to the meeting two or three days ago on the whole question of cell substrates. This is a crucial issue for anyone responsible for R&D and R&D investment.

I'm sure that it is clear to you all, it was very worthwhile to attempt to get consensus between, on the one hand, government agencies, government bodies such as NIH, such as NIBC, Paul-Ehrlich and others, as well as academia, and, indeed, the industry, and the agency is, I believe, to be commended on that.

It is important to look at risks, as has been said. It's also important to look at benefits, and I'm sure I needn't remind this particular committee that vaccines have been undergoing quite some reconceptualization and broadening, seeing them both, on the one hand, as prophylaxis, and in that sense prevention of disease, and on the other hand as immune modulators, and to some degree treatment of infectious diseases. So, the roles are shifting with time.

For those of us attempting to invest and

decide on investments in these areas, one of the most important things for us is to know what it is we are trying to aim at, what consensus is amongst agencies as to what we should be doing, and it's particularly important to hear those consensuses reviewed and endorsed by a committee such as this, when, indeed, it comes back to you.

I would, indeed, point out that when the study is done a great deal of work has clearly gone in before, I hope the committee will give it clear recognition, and I believe that the agency, FDA in this particular case, is to be commended on making the effort to push for this. I hope the committee understands just how much is involved in that.

Thank you for your time.

CHAIR GREENBERG: Do committee members have any questions of Doctor Young?

If not, thank you, Doctor Young.

Is there anybody else in the audience who wishes to address the committee?

Let the record show that I've stared down the audience and nobody seems to be raising their hand.

If that's the case, I am going to recommend that we take a break now, end the open

public hearing, and I'm told that several of the committee members have yet to check in, so what I think I will do is, let me just look here, I think we will get back on track, and can people check in in a half an hour? So, I'd like people back here at 3:45, to start again promptly at 3:45. At that time, we'll start our closed sessions, and, in fact, Doctor Daum will start that session because I will be not in the room.

EXECUTIVE SECRETARY CHERRY: Yes, and we will be in closed session, so at this time I'm afraid we'll have to dismiss the audience.

(Whereupon, the open session was concluded at 3:16 p.m.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: MEETING SESSIONS 1 THROUGH 4

Before: VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

Date: SEPTEMBER 14, 1999

Place: BETHESDA, MARYLAND

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