UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
ALLERGENIC PRODUCTS ADVISORY COMMITTEE MEETING
(APAC)

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Friday
March 15, 2002

The Committee met at 8:00 a.m., in Versailles Rooms I and II of the Bethesda Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland, 20814, Dr. Samuel B. Lehrer, Chairperson, presiding.

COMMITTEE MEMBERS:

SAMUEL B. LEHRER, CHAIR, Ph.D.
MELVIN BERGER, M.D.
A. WESLEY BURKS, M.D.
WILLIAM FREAS, Ph.D.
REBECCA S. GRUCHALLA, M.D., Ph.D.
PETER HAUCK
DOLORES LIBERA
SUSAN M. MacDONALD, M.D.
HAROLD S. NELSON, M.D.
MARIA C. SOTO-AGUILAR, M.D.
DALE T. UMETSU, M.D., Ph.D.

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

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

(8:11 a.m.)

DR. FREAS: Good morning. I would like to welcome everyone to this 18th meeting of the Allergenics Products Advisory Committee. I am Bill Freas. I'm the Executive Secretary and I'll be introducing the speakers at the main table. Most of the meeting today will be open to the public. However, there will be a short closed session as announced in the Federal Register. This session is closed to discuss personnel issues of a site visit report of the Laboratory of Immunobiochemistry.

Now, before I introduce the members at the table, I would like to say that we had a meeting this time last March, excuse me, this time last year in March and the East Coast was hit by a terrible severe winter storm and two of our new members could not make it. Therefore, I'll be introducing to you six new members this morning and a welcome to all of our new members.

I will start going around the table and introducing everyone, including the old members as well and I'll identify the new members as we get to them. Starting on the right side of the table, that's the audience's right side, we have a long time member,

Dr. Dale Umetsu, Chief Division of Allergy and Clinical Immunology Stanford University. And would the members just raise their hands so the people can see who is who, especially myself.

Sitting next to Dr. Umetsu is one of our new members, Dr. Rebecca Gruchalla, Assistant Professor of Internal Medicine, University of Texas, Southwestern, Medicine. Welcome. Next is another new committee member, Dr. Harold Nelson, Senior Staff Physician, Department of Medicine, National Jewish Medical Center. Next is our consumer representative, Ms. Delores Libera, Director of Publications, Allergy and Asthma Network and Mothers of Asthmatics, Incorporated, Fairfax, Virginia.

Around the corner of the table we have another new member, Dr. Melvin Berger, Professor of Pediatrics and Pathology, Case Western Reserve, School of Medicine. In the center of the table, we have our Chair, Dr. Samuel Lehrer, Research Professor of Medicine, Tulane University Medical Center. Around the corner of the table, we have another new member, Dr. Susan MacDonald, Associate Professor of Medicine, the Johns Hopkins University School of Medicine.

Next we have another new member, Dr. Wesley Burks, Professor of Pediatrics, University of

Arkansas for Medical Sciences. Next we have a standing committee member, Dr. Maria Soto-Aguilar, a physician in private practice in Hudson, Florida, specializing in allergy, rheumatology and immunology. Next we have not only a new member, we have not only a new member, we also have a new position on this committee. The new position is that of a non-voting industry representative and that position is filled by Peter Hauck, who is Executive Director for Scientific Affairs of the Allergen Products Manufacturer's Association.

Welcome to all of the members, especially the new members. I would also like to thank Pearline Muckelvene who the members have been coordinating with in the last couple of months who has organized and pulled this meeting together. She is outside of the table in the back.

Now, I have to read into the public record conflict of interest statements for this meeting. The following announcement addresses the conflict of interests issues associated with this meeting of the Allergenic Products Advisory Committee on March 15th, 2002. "To determine if any conflicts of interest existed, the Agency reviewed the submitted agenda and all relevant financial reported -- interests reported

by meeting participants. The discussions at today's meeting are considered general matters issues.

The discussions will effect all firms involved equally. Therefore, no products are being discussed at this -- no specific products are being discussed at this meeting. We would like to note for the record that Peter Hauck is participating in this meeting as an industry representative acting on behalf of a regulated industry. Mr. Hauck has the following interests.

He is Executive Director of Scientific Affairs, Allergen Products Manufacturer's Association. He also has relationships with numerous firms involved with allergen extracts. In the event that the discussions involve products or firms not on the agenda for which FDA participants have a financial interest, the participants are aware of the need to exclude themselves from these discussions and their exclusions will be so noted for the public record.

With respect to all other meeting participants, we ask in the interest of fairness that you state your name, affiliation, and any current or previous financial involvement that you may have with any firm whose product you wish to comment upon". That ends the reading of the conflict of interest

statement. Dr. Lehrer, I turn the microphone over to you.

DR. LEHRER: Thank you very much, Bill. I want to welcome first all of the members and particularly the new members. I know with this day and age of travel, it is a real effort to get anywhere nowadays and your service certainly is greatly appreciated. I wanted to also welcome the public that's attending the open session and I wanted to give a thanks to the staff, especially to Pearline Muckelvene for all the help that they provided in preparing for this meeting.

Today I think all of you should have copies of the agenda listing the topics that we're going to discuss and I'm not going to review them in detail, just to make some brief remarks. And what we're going to do is cover some of the activities that have been done over the past year at the laboratory. And that will consist of much of the morning's session, it will be an open session.

Then there will be several regulatory topics that we will discuss in the afternoon following lunch. This will be an open session as well and there will be opportunity for the public to comment and then finally, we'll go into closed session in which we'll

consider the site visit report and that will be discussed and then we will adjourn.

I really don't anticipate this lasting longer than the adjournment time, which is at 4:00 p.m. and perhaps it may be sooner but a lot depends on how the discussions go. So again, welcome everyone and now we can begin with our session.

The first presentation will be by Dr. Richard Walker, who is the Division Director and this is the -- he will present an overview of his division, the Division of Bacterial, Parasitic and Allergenic Products. Dr. Walker?

DR. WALKER: Good morning. Thank you. This morning it will be my pleasure to introduce the Division of Bacterial, Parasitic and Allergenic Products to you. What I will try to do in the next 15 minutes is introduce you to the roles and challenges of the research reviewers which make up our division and also talk a little bit about how we're organized to meet these challenges that our division must deal with.

Basically, all of the laboratories, and there are eight laboratories in the Division of Bacterial, Parasitic and Allergenic Products, all our laboratories have the mission to assure safe and

effective products for immunological control of bacterial, parasitic and allergenic agents affecting human health. And as I've already indicated we have researcher reviewers in our division so these people conduct research in the laboratories as well as conduct review functions for the various sponsors for our products.

Something that I'm going to emphasize is that not only do we review products during their development and going through licensing but our interaction with a product continues to post-licensure surveillance, and as you can see on this slide, inspection issues, lot release and label and promotional activity review are all part of our functions.

In addition to these functions dealing directly with products, we also are involved in numerous consultations with other organizations like PAHO and WHO and different agencies of the U.S. Government and so forth dealing with vaccine issues. This slide and the slide that follows it is just trying to drive home one thing and the bottom line is not all of the things in the vertical columns on this slide but the horizontal and once again, I want to emphasize that our research reviewers become involved

with a product usually early in its life as shown here, like in the pre-IND phase where we've begun meeting with the sponsors, talking about the product and provide some guidance, but it also goes through the IND phase where we're looking at the review of the original submissions, we're giving technical advice for product assay and development and so forth, then on in through clinical testing into pre-licensure review of final product manufacturing processes and so forth.

But the key thing that I'm emphasizing one more time is that it's a lifelong interaction that we have with the product that goes post-licensure as shown in this slide where we're doing things, looking at deviation reports, view of post approval commitments and so forth. So it's a very involved and long term process that we have with the product.

The other part of the challenge facing our researcher reviewers is the number of products and the variety of products that they have to deal with. This slide and the next slide just put together a number of products that might be possible within the next 10 years that could either be -- existing products that could either be improved upon or new products that need to be developed. As you can see, we have

respiratory pathogens all the way from things causing earache to pneumonia, sexually transmitted pathogens, pathogens encountered through a bite, like by a mosquito or a tick and then in the last couple of years, and particularly since this last fall, we're looking at issues dealing with products for special pathogens, bioterrorism agents, like Franceisscella tularensis, Bacillus anthraces, Clostridium botulinum and Yersinia pestis.

In addition, we're looking at not only newer pathogens like these bioterrorism agents but some very old pathogens, like those that cause diarrhea, diarrheal diseases for which we don't have licensed vaccines at the moment, other mucosally trafficking pathogens, like Helicobacter pylori which has recently become recognized as a major human pathogen and of course the focus of today's meeting is our allergenic products dealing with a variety of issues and products such as latex and cockroach antigens and so forth.

And then we also have skin test antigens that people in our division are involved in review or regulatory activity such as PPD, Coccidian and so forth. So we have a long-term involvement with a product. We have quite a variety of products and our

division is organized into eight laboratories to deal with all of these products. I'm in the, of course, the Immediate Offices of the Director and I'm not ignoring my Deputy Director. Right now I don't have a Deputy Director. I have a vacancy and that's one of the reasons I won't be able to spend this morning with you because I'm trying to play the game of being everywhere at once but then my job and the other people in our immediate office staff are dedicated to try to help these other people accomplish their jobs in the various laboratories.

So as you see starting at the top over here on your left, we have the Laboratory of Respiratory and Special Pathogens, the Laboratory of Bacterial Toxins, the Laboratory of Microbacterial Disease and Cellular Immunology, Laboratory of Methods Development and Quality Control, Laboratory of Immunobiochemistry that we'll be focusing on today, that's Dr. Slater's laboratory, the Laboratory of Biophysics, the Laboratory of Enteric and Sexually Transmitted Diseases and Laboratory of Bacterial Polysaccharides.

Now, what I want to do in the remainder of my talk is sort of go through what goes on in these various laboratories. Now, these laboratories are

abbreviated in red on this slide, like the LMDQC and so forth, and it's not so important what each one of those abbreviations stands for but if you take all the talent and the resources that are present in these various laboratories, we can bring them to bear on various focus areas and that's what I'm showing on this slide, that one of the things that all of the laboratories are involved in to some extent or another is standardization of assay methods for these various products that we deal with and the laboratory methods development and quality control is one of the major laboratories leading this process.

Another major focus areas is pertussis and other toxin mediated diseases, like tetanus and diphtheria. Then we have another focus that doesn't have as many laboratories involved in it, but is focused on the microbacterial diseases and other intercellular parasites. Then a newer area or an area that we've had for some time but we're building up is mucosal pathogenesis and immunization because so many of the pathogens that I showed you on a few slides back are mucosal pathogens. And also we're interested in trying to get to needless type delivery systems, so we're trying to understand how like oral immunization might be accomplished.

Another major focus area that, of course, we'll be talking about today is allergenic products and allergenic diseases, as I've already alluded to, our newer focus area, which is products to combat bioterrorism agents. So just very briefly, I'm going to run through these eight laboratories just to give you a flavor of the overall division of which the Allergenics Group is a part.

The Laboratory of Methods Development and Quality Control, as you would expect from the title is focused in the development of standardization and quality control methods for bacterial vaccines. They develop immunologic type methods to assure the immune response or quantitate the immune response in vaccine trials. And then as I've already said they've taken the lead in our effort within the Center for Biologics Evaluation and Research to develop a quality assurance activity and so this laboratory within our division provides our divisional leadership to get us accredited for quality control testing.

The Laboratory of Bacterial Polysaccharides is also involved in some testing like standardization methods for relevant clinical applications, development of novel physical and chemical methods for improved evaluation of licensed

and experimental vaccines that involve Polysaccharides or conjugate vaccines but they're also involved in research activities such as characterization of immune responses to polysaccharide and conjugate vaccines as well as trying to characterize innovative -- characterize vaccines and develop innovative approaches to development of new vaccines and also an evaluation of epidemiologic aspects of various vaccine candidates.

The Laboratory of Biophysics is a group that uses high tech instrumentation and modeling to study or plot various molecules of import in vaccines and immunologic agents. They have been involved in studies already of characterization of biopolymers, such as Polysaccharides, proteins and DNA and macromolecular assemblies such as vaccine/adjuvant complexes and membranes and so forth. They use, as I said, various high end instrumentation such as NMR and light scatterings and so forth to provide a characterization of various products.

The Laboratory of Respiratory and Special Pathogens is conducting structure and function studies of various toxins, particularly pertussis toxin and they're investigating the molecular biology or the regulation of virulence factors of not only pertussis

but also a lot of our anthrax research goes on in that division. And they're developing animal models for evaluation of various aspects of pertussis infections.

The Laboratory of Bacterial Toxins is involved in a variety of studies, characterization of Tetanus toxin also there's an interest in that group in iron-related virulence determinants as C diptheriae and bacillus anthraces and also doing some work with the biosynthesis of bacterial Polysaccharides. And there's also new work going on in there that's just started. I'll have to update these slides.

They are also doing much expanded work on Botulinum toxin now.

The Laboratory of Microbacterial Diseases and Cellular Immunology is evaluating immune responses to intracellular bacteria. They've been concentrated not only a tuberculoses but also on Franciscella tularensis. They're assessing DNA vaccination strategies against TB and they're also trying to identify different proteins that might be useful in vaccines against TB.

The Laboratory of Enterics and Sexually Transmitted Diseases is looking first at invasion mechanisms of certain of the enteric pathogens such as C. jejune, Shigella species and also Salmonella.

These organisms all colonize and then invade. They're also looking at genetic regulation of various surveillance factors and have been doing some work, even though that work has just shifted to our Laboratory of Bacterial Polysaccharides have been looking at hormonal effects on gonococcal pathogenesis.

They're also studying as I indicated is very important a little while ago, how to better achieve mucosal immunity and how to does for effective mucosal immunity and maybe how adjuvants might be used for that. They're also doing some work on anthrax using mucosally delivered anthrax antigens.

I'm not going to say too much about this laboratory because you're going to be hearing a lot more about it this morning. Our Laboratory of Immunobiochemistry is looking at allergen structure and function, immunomodulation of the allergic responses and chemokines and chemokine receptors in the modulation of immune responses. I think it's very important that we have this strong immunological emphasis in this laboratory, but as I said, you'll hear a lot more about it this morning.

The final thing that I want to show you is just because I've been emphasizing how a lot of our

activity within the Division of Bacterial, Parasitic and Allergenic Products has become focused even more so than it was in the last two years, it's been focusing more so recently on bioterrorism. So right now we have research and review going on in our division for both -- not only bacillus anthraces which was our original focus as far as bioterrorism, but recently we've expanded that to more extensive studies of Franciscella tularensis, new studies of Yersinia pestis and expanded studies Botulinum toxin. Once again, we're using the various approaches that we've used on these other pathogens like genetic manipulation and regulation, the study of virulence factors, examining ways that vaccines might be improved and standardization assays that could be used in regulating products for these types of agents.

So this should give you an overview of the challenges facing this division, the nature of the work done by the researcher reviewers and sort of an overview of the organization and how -- and what we do in the various aspects of the organization to help meet these challenges.

One final thing, I'd like to leave you with is these people you'll hear this morning when you hear some more of the details. In Dr. Slater's work

you'll see the quality of their work. I want you to keep in mind that these people are conducting world class research programs. At the same time, they're conducting review activities which can take up to 50 percent or more of their time and another aspect of these review activities it puts a challenge on our researcher reviewers is that these people have no control over the scheduling of these activities. They don't know when a sponsor submission is going to arrive and then they'd have certain time limits that they have to deal with that product.

So these people are under a tremendous time pressure and have a tremendous responsibility. I think it's remarkable that they accomplish not only their review activities, but they accomplish world class research. Thank you.

DR. LEHRER: Thank you very much, Dr. Walker. Do any members of the committee have any questions for Dr. Walker? Any members of the public have any questions or comments?

Thank you very much.

The next presentation will be an overview of the Laboratory of Immunobiochemistry by Dr. Jay Slater, the Laboratory Chief. He will discuss personnel and organizational and lot release

activities. Dr. Slater?

DR. SLATER: Thank you very much. I want to start by echoing the thanks that you heard from others for coming. I really appreciate -- we really appreciate the time and effort you're putting in. Two of you were here for the site visit in January. Most of you were at the Academy meeting just a couple of weeks ago. Now, you're all here. It's a lot of time, a lot of travel. We really appreciate the time and the effort that you're putting into participating in this committee's activities.

Today in the open session, I'm going to start with a lab overview and then we'll do an update of the research activities of the laboratory and this year the research update is going to be a little different than it has been in past years because of the site visit and what I'm really going to do is give you a brief summary of the site visit overall presentation that I gave back in January.

My plan was to have Dr. Rabin present his project in somewhat greater detail since he's the new person in the laboratory but Dr. Rabin, unfortunately had to be out of town on a personal family emergency and so he will not be making that presentation today. What we're going to talk about next is a couple of

regulatory updates, the first one about particulates in allergen extracts, which we presented in somewhat greater detail at last year's meeting but we have some additional information and as part of that, Teddi Lopez from the Compliance Division is going to be giving you an update on compliance activities of the FDA in the allergenic industry over the past year.

We'll also be giving you an update on the transmissible spongiform encephalopathies. Again, last year I presented in somewhat agonizing detail our analysis of the issues regarding allergenic extracts. This will be a much shorter and more succinct presentation of some of the material from last year as well as some updated information of what's happened in the past year.

Then after those two update presentations, I'll be making a presentation about recombinant allergens and the purpose of that presentation is really to sort of initiate a discussion within the committee on issues that I suspect we're going to be confronting over the next several years and in addition, I'm going to be giving a review of the role of glycerol in allergen extracts. Not much new material there but this is something that has come up recently, particularly in reference to particulates

and I thought this would be an opportune time to review one of the reasons that glycerol is such an important component of allergen extracts, at least in the United States.

So let's talk about some of the operational issues of the laboratory and again, I'll be going over this history of the laboratory and some other structural issues later on. This is just an update, a snapshot of where we are now. We have three principal investigators in the laboratory. I've been in the lab for three and a half years. Dr. Lyudmila Soldatova has been in the laboratory for four years and Ron Rabin really started just before last year's advisory committee meeting. He's been there the shortest time.

We have two post-doctoral fellows. Jonny Finlay came about 14 months ago and Hui Huang came even more recently than that. We have six research technicians who also -- five of whom also wear the hat of regulatory biologists and microbiologists; Melissa patters, Al Gam, Mona Febus, Marc Alston, Cherry Valerio and Katia Dobrovolskaia is an IRTA technician. She doesn't participate in regulatory activities but spends 100 percent of her time on research. And in addition, we have three guest workers, Bhavini Trivedi

is an NIH fellow who's working with us this year, Gerry Poley is an allergist from Children's Hospital who works -- does research at our laboratory and Li-Shan Hsieh actually works in Cedar but also does part time research in our laboratory.

And my computer just froze. It's probably because of the ornate graphics of this incredible picture that I've showed year after year, which basically gives you an idea of where our staffing has been since I came to the laboratory and the staffing on this graphic it really focuses on the regulatory staffing, the research regulatory technicians that we have and the bottom line is that we are now up to what I think is a very stable, reasonable level in terms of performing the regulatory activities of the laboratory.

We've certainly had our ups and downs and we've been lower in the past than we are now but we have a very good crew and are very comfortable with out level of staffing in the laboratory at this point.

In addition to the research activities that you're going to hear more about in a few minutes, we have a number of regulatory activities that I put routine in quotes because although some of these are routine activities, they often are not and we often

have to respond to immediate situations as they arise, but we are responsible for reviewing the lot release data that manufacturers send us on every lot of standardized allergen extracts in the United States.

We also do testing on those lots to confirm the manufacturer's data. We are responsible for the U.S. Standards of Reference and we're responsible for developing those references, maintaining the references with semi-annual checks and replacement and in addition the distribution of those references to the manufacturers so that they can use them for their lot release activities.

We reviewed in the year 2001, we reviewed 406 protocols, each of them for a different lot of standardized allergen extract. We tested a number of them. We reviewed all of them and two of them, in fact, were withdrawn for lot release failure, evidence of lot release failure. We distributed 2,151 vials of U.S. Reference Standards and 101 shipments are sent to our manufacturers for their lot release activities.

We replaced two references this past year, E4 cat was replaced in April. The process of replacing a reference involves screening the references that we have, choosing a reference that looks like it will be closest to the current U.S.

Reference Standard and cause the least disruption when we switch references. Then what we do is we purchase a significant amount of the reference and send it out to the manufacturers so that they can test.

We send it to all of the manufacturers. We give them 60 days to send us back their results and then we pool the results, decide whether the reference is, in fact, a good one, the candidate reference is, in fact, a good one and then we select it as the next U.S. reference standard. If based on our analysis of the manufacturer's data combined with our data, the reference does not seem to be a reasonable change from the previous U.S. Reference Standard, then we reject that candidate reference and start the process all over again.

This year we didn't have to reject the references. Our candidate reference for E4 cat hair was distributed in April. Seven manufacturers responded and we finally shipped out the new reference in July. C10 cat which is the calibration curve that was made out of E4 cat hair, was sent to the manufacturers for testing in August. Five manufacturers responded with their data and we sent out the new calibration sets in November.

We have had several publications this

year, although this hasn't been our strongest year in terms of publications. I'm optimistic about next year. Melissa Patterson and I wrote an article about our work on cockroach allergens, which actually I presented in large measure at last year's advisory committee meeting, that was accepted by Clinical and Experimental Allergy and is currently in press.

A paper that was written by my collaborators in Melbourne, Australia using reagents and collaborating with them on work on specific monoclonal antibodies in human IgE studies of Hev b 5, responses, that's also in press in Clinical and Experimental Allergy.

We published two reviews this year, one of them Kristin Morrow, who's no longer with the lab and I wrote in Clinical Reviews and Allergy and Immunology on regulatory aspects of allergen vaccines in the U.S. In addition, I just finished co-authoring the chapter called "Preparation and Standardization of Allergen Vaccines" in the upcoming edition of Middletons' textbook.

We were very active at the Academy meeting this year. We had seven abstracts, six of them were poster presentations. One of them, Ron Rabin's, was an oral presentation. And that is all I have for the

lab overview.

DR. LEHRER: Are there any questions from the committee members?

DR. MacDONALD: Thank you, Jay. I have a question. Being an academic and doing clinical related research, what is the timeliness for the FDA to respond to academic queries of when you would like to use a reagent and is there a necessary time limit that the FDA can respond to the investigator?

DR. SLATER: Well, we attempt to respond as quickly as we possibly can. I don't know that there's any specific mandatory time limit in terms of those responses. There are time limits in terms of other formal responses to INDs and to BLA supplement applications and BLA applications. And since there are -- there are clear and hard limits imposed on those, very often those will take -- those activities will take priority.

But we certainly attempt to respond to all queries as quickly as possible. You know, those queries come in many different forms. Some of them are voice mail messages left on machines and others are more formal requests but we certainly make an attempt to respond as quickly as possible to those.

DR. LEHRER: Related to that question, do

you have any information on how either response times or you mentioned lot release activities and referenced distributions and so on, compared to previous years?

DR. SLATER: We haven't been tracking that. I can tell you that we -- with lots submitted to us for lot release, the laboratory responds, you know, within -- certainly within 10 days at the outside and most of the time much more quickly than that. In the lot release, the lot release paperwork has to go through several steps before the manufacturer is finally notified that they can release the lot so there are several steps involved. But we do make a concerted effort to get those out quickly because we know the manufacturers are eager to release the lots.

DR. LEHRER: What I was getting at is with the increase in personnel and it seems that the laboratory is functioning better than it ever has, would you say there is an increased or more rapid response compared to previous years?

DR. SLATER: Well, I would hope so. I mean, I can only gauge it by the number of complaints that I get. You know, no one sort of tells me I'm doing a great job and my lab is responding quickly but I think that with the increased staffing, we certainly

respond very quickly to inquiries from the manufacturers. They all know how to reach the people in my lab directly. They also all know how to reach me directly and I think the communications are fairly open and fairly rapid. And certainly in terms of turnover time for lot release, I suspect we're doing better but I don't have real data to demonstrate that.

DR. LEHRER: Thank you. Any other questions from members of the committee?

DR. MacDONALD: I have a question about the response of the manufacturers. How do you determine how many manufacturers need to respond before you can release a lot?

DR. SLATER: We consider the step in which we send the lots to the manufacturers a critical step in terms of our ability to collect as much data as possible and really ascertain that the new U.S. Reference Standard is statistically identical to the old U.S. Reference Standard. We don't have any arbitrary cut-off and theoretically if the -- if none of the manufacturers responded, we would still make a decision just based on the data that we have

I should tell you that we do a lot of in-house data. We do a lot of work on these references before we send them out to the manufacturers. So it's

not as though we don't have any data but sometimes we have found that the manufacturers who really are going to be working with these references as much or even more in some cases than we are to make some new observations.

Every year I try to encourage the manufacturers to respond, all of the manufacturers to respond and I think our response rate, in fact, has gone up over the past year. I think these numbers are better than they have been in the past. But I agree with you. I think it's an important step. When we replace a reference we're not in the position to not release the new reference based on a lack of cooperation or lack of participation from the manufacturer. So we really need to make a decision based on whatever data we have. Obviously we welcome having as much data as possible.

DR. LEHRER: Yes.

DR. EAGAN: Yeah, I'm Dr. Eagan, the Deputy Director for the Office of Vaccines. I'd just like to make a couple of very quick comments about the lot release program just to amplify a little bit about what Jay said and note that it's a coordination between several offices and many different labs, so it's not just Jay's group.

Samples come into our Office of Biologics Quality Control. They get logged in and then several different reviews will start. Some will be done in Jay's lab and some will go to other laboratories within the Office of Biologics Quality, and Chris Anderson's lab, for example, or Joe Jay's lab, depending on the nature of the test whether tests for sterility or particular preservatives or glycerol or what have you and then part of that is in Jay's.

And then everything is assembled and then it goes back to Jay Elterman in the Office of Biological Quality. And there the protocols will be signed off on if they're approved and then the lots get released, so it's a rather complicated process and it involves a number of people.

I'll mention that very recently, however, two of the laboratories that are involved in biologics quality control that is Chris Anderson's group and Joe May's group, they have just recently been or are in the process of being transferred over into the Office of Vaccines and one final comment, one of the areas that we're looking at now are various ways to speed up the lot release program.

DR. LEHRER: Thank you very much. I think we can move onto the -- yes, one last comment.

DR. UMETSU: I was just wondering what kind of data do you collect about these lots? I heard about the sterility but what other data do you look at before deciding to release a lot?

DR. SLATER: It depends on the lot itself. Lots that contain 50 percent glycerol, the manufacturers have to test to ascertain if the glycerol content is within error limits around 50 percent. They have to be tested for phenol content. If they're lyophilized, they have to be tested for water content. There's sterility tests, potency tests, identity tests. There's a menu of tests that's actually unique to each product that -- and the only tests that are handled by my laboratory in fact, are the tests for potency and identity and the rest of the testing is handled in other laboratories.

DR. LEHRER: Okay, I think we can get onto the next topic. This will again be Dr. Slater, who will review or update is with research activities.

DR. SLATER: Thank you. This is actually a short summary of the site visit presentation on January 24th. The Laboratory of Immunobiochemistry has gone through several iterations over the years. It was in the past the Laboratory of Allergenic Products, which in a sense is probably a more

descriptive and accurate name within the Division of Bacterial Products.

Subsequently, it was -- the name was changed to the Laboratory of Immunobiochemistry and this was now within the new Division of Allergenic Products and Parasitology. And within the Laboratory of Immunobiochemistry there were two distinct but organizationally connected laboratories. One was the Allergenic Products Testing Lab and the other was the Allergenic Products Research Lab. Three years ago, the Division of Allergenic Products and Parasitology merged with the Division of Bacterial Products into the new larger and very happy Division of Bacterial, Parasitic and Allergenic Products and at the time that I came on board, we retained the name of the Laboratory of Immunobiochemistry but eliminated the distinct research and testing laboratory programs within the laboratory.

The mission of the laboratory is to support the regulatory mission of CBER and FDA in assuring the safety and efficacy of allergenic products in the United States and we do this in five ways. We do it by performing original research in the field of allergen structure and function and immunomodulation. We also respond to specific

regulatory needs with directed research projects. We provide expert advice and support for CBER, FDA staff regarding allergy and allergenic products.

We review, confirm and approve lot release data from allergenic product manufacturers and we assist in the review of BLAs, those are biological license applications and INDs, investigational new drug applications, that relate to allergenic products.

Now, I had looked for a floor plan of Building 29 at NIH and couldn't get one, so I used the floor plan of my own house and superimposed these numbers on it. LIB is lucky enough to be on the NIH campus in Building 29 in the basement and on the second floor. We have an office/library complex in Room B1, a laboratory in Room B3. This is where Ron Rabin, Jonny Finlay, Hui Huang and Bhavini Trivedi do most of their research.

On the second floor, my office is in Room 203. We have a large laboratory at 214 to 218 complex in which most of the other work is done. Room 211 is also a laboratory and 212 is a lunch room and office. We are a very well-equipped laboratory for what we do. We have all of the standard equipment that you would expect in a biochemical and immunologic laboratory. We have some equipment that you might not be lucky

enough to find.

We have a mouse plethysmograph, a non-invasive buxsco mouse plethysmograph in our lab. We have an excellent fluorescent imager and with Ron Rabin's arrival, we obtained a magnetic cell sorter and the Division, in concert with the Division of Viral Products purchased a flow cytometer that's housed on the fifth floor but that is readily accessible and is actually largely used, at this point, by Dr. Rabin and Dr. Elkins.

We also have terrific core facilities at CBER. Most of these are located in Buildings 29 and 29A, which immediately adjoins our building. Some of them are located in the Nicholson Lane facility which is about three and a half miles up Rockhill Pike. These include a DNA sequencing facility, oligo primer synthesis, peptide synthesis, N-terminal sequencing, mass spec analysis, amino acid composition and lyophilization core facility.

There's also a substantial amount of really topnotch shared equipment and it's readily available to us. There's a gene expression microarray laboratory, there's a circular dichroism spectrometer in Building 5, which we've actually used quite a bit over the last year and there are currently two NMR

spectrometers of 300 and 500 MHz with a third machine, 700 MHz on order and due for arrival fairly soon.

The scientific goals of our laboratory are really three-fold. We look at allergen structure and function, the immunomodulation of allergic responses and this is clearly the most regulatory focused scientific goal, the preparation and preservation of allergen reference standards.

And in order to illustrate how each of the projects ties into these goals, I've put together this cartoon graphic with each of the three goals in the three corners of a triangle. The latex cockroach hymenoptera work that we do really fits neatly in between these two goals as I think does Ron's work on RVS and MDR, work a little bit closer perhaps to the immunomodulatory goal than the allergen structure and function goal but nonetheless, located between those two goals.

The work that I've been doing on the effects of lipopolysaccarides on allergic responses clearly fits closer in between these two goals. Our concern, obviously, is that there is and we know there is endotoxin present in allergen extracts, and we're concerned about the effects, either positive or negative that this may be having on the use of these

products as immunomodulatory agents.

We have a project in which we've been looking extensively at the effect of lyophilization on the stability of allergen extracts and that clearly fits closest to this goal. This is an example of a minor project that's been driven by regulatory necessity. The presence of precipitates in allergen extracts which I will be talking about in more detail later, is a project that fits in between these two goals.

We had some work that went on over the last couple of years using novel techniques of characterizing allergen extracts both MALDI-TOF and SELDI technology in the identification of allergens that ties in fairly closely with that goal. Jerry Poley's work on the cross-reactivity between foods and latex, obviously fits between these two goals and a recent new project on the study of protease activated receptors on mass cells fits closest to this goal.

Now at the site visit we didn't talk about all of these projects. We actually focused on these projects at the site visit and it had been my intention to focus on these two projects today with Dr. Rabin's presentation. What I'm going to do in response to his absence today is I'll cover some of

the other projects in somewhat less detail.

It's important to note that as Dr. Walker mentioned, we have a research program that we're very proud but our mission in essence, a regulatory mission and it's important to note that each of our research projects really ties in fairly tightly, I think, to a specific regulatory objective of the laboratory either looking at latex cockroach hymenoptera, in terms of what we anticipate is going to be our regulation of recombinant allergens and examining novel immunotherapy options.

Our studies of lipopolysaccharide in allergen extracts clearly is looking at the safety and efficacy of allergenic products. Extract potency determination methods ties in fairly closely with our lot release activities. Extract preservation, the lyophilization study is really largely our effort to replace lots less frequently. It would be much less disruptive if we could develop a U.S. Reference Standard that would be good for 10 years rather than three, four or five years and this is our objective in this study.

Ron's work on RSV and multi-drug resistance proteins is clearly looking at immunomodulation in a novel and I think, a very

interesting way. In addition, when building this laboratory as it's been my privilege to do over the last three and a half years, I've been paying attention to our technical capabilities and to the interactions of the different parts of our laboratory in terms of the technical capabilities and the contributions that one project can make to another.

So you know, clearly for the latex and hymenoptera projects, we've been using standard techniques of protein analysis, DNA analysis and cloning and mutagenesis. The work on cockroach allergens has introduced some novel techniques into the lab. We've been constructing combinatorial IgE libraries. The LPS study, the novel contribution of that to our lab has been a study of mass responses using plethysmography and Ron's work has introduced flow cytometry and cell sorting to the laboratory, but clearly we've been using the techniques from the latex and hymenoptera studies for our cockroach work.

Likewise Jonny Finlay's work with the combinatorial IgE libraries will clearly have applications to our latex and hymenoptera work. The plethysmographic skills that we've been developing with the LPS study are also going to be applied to latex and hymenoptera and Ron's skills with flow

cytometry and cell sorting are going to have broad applications to, I think, all of the other projects in our laboratory.

Again, to emphasize the point that all of our biologists who can participate in research and regulation do both. Each of our biologists has a primary area of research activity and several of them have secondary areas of research activity as well.

So at the site visit, we -- Dr. Rabin, Dr. Soldatova and I presented key aspects of our various projects and I'm going to take advantage of Dr. Rabin's absence now to give an extremely brief summary of each of those projects without audio-visual benefit.

Ron's work on the characterization of responses to RSV by T-cells from human tonsil really, I think reflects a novel approach to the question of how TH_1, TH_2 polarization happens in vivo and what the possible influence of viral infections on that might be. He is going to be obtaining tonsils from children, putting those into histoculture, infecting them with RSV and looking at both the cytokine responses of those cells and the phenotypic responses of those cells.

He's very experienced in doing both of

those and that project is actually going forward very nicely already and is, I think, one of the most exciting projects in the laboratory. Working with Dr. Hiu Huang, the second project, the modification of the multi-drug resistance protein activity as a potential mechanism of immunomodulation is also a novel and exciting project. It borders on the medium to high risk project because it's really based on an interesting observation and, you know, I think it's very likely to be successful.

Multi-drug resistance proteins, as you all probably know, are ubiquitous membrane proteins that have been extensively studied as potential agents of chemotherapeutic resistance and targets for enhancing chemotherapy in cancer studies. What Dr. Rabin observed a couple of years ago is in his studies of Waggoner's granula metosis cells, that they had evidence of impaired MDR protein activity and he wondered whether MDR could actually be or MDR type proteins could actually be involved in lymphocyte activation and with Dr. Huang, they're actually developing the tools now to look at this carefully in lymphocytes.

It's actually a very exciting project, again, like his other project, looking at sort of a

standard question in a novel way and I think it's going to go very well.

Dr. Soldatova at the site visit presented two of her projects. Dr. Soldatova has been a scientist who's been committed for many years to the study of bee venom allergens and the work that she presented included her study on the glycosylation and the allergenicity of bee venom hyaluronidase using recombinant hyaluronidase expressed both in E-coli and in bacculovirus infected insect cells and comparing their activity, comparing their enzyme activity.

In addition, she's been looking at mutants of hyaluronidase that have been mutated both in the enzyme active sites and in each of the four N-glycosylation sites and looking at again, the antibody binding and the enzymatic activity of these mutants. In addition, she has cloned a new vee venom allergen, acid phosphatase and has obtained the sequence for the allergen.

Now, I just said that in two sentences. That's been a lot of very hard work involving the dissection of venom sacs from over 500 honey bees and the extraction of RNA from those, the construction of a cDNA library that ultimately led to the obtaining of the full sequence. So those projects are also

described in the site visit briefing document that you've been sent. And those are projects that are going forward very well, as well.

At the site visit in January, I presented three of my projects. The first is the look at LPS, defective LPS on allergenic responses and this project has sort of two wings to it. One wing is a study that we started at Children's about five years ago in response to inquiries regarding the observation that latex gloves had a significant amount of endotoxin and we were able to demonstrate fairly clearly in mice, that LPS enhanced IgE responses to the latex allergen Hev b 5.

When I came to FDA we attempted to replicate this with ovalbumin and found that we could easily replicate that and we subsequently found that if we introduced the allergen and the LPS into the airway as opposed to just into the nose, we also could elaborate a very high level bronchospastic responses as well. So one angle on this is to look at the mechanism of LPS' effect on allergen responses in these mice and that's going forward actively. But another interesting angle on this project is one that Dr. Trivedi is now following.

She went back and looked again at commonly

used allergen extracts that had been shown many years ago to contain endotoxins and she looked again and found, once again that house dust mite and cat extracts at least contain significant quantities of endotoxin although highly variable from one manufacturer to another.

She's now in the process of looking at whether those amounts of endotoxin are significant in terms of the responses first of animals and ultimately we will be comparing human immunotherapeutic responses to different licensed products that contain different amounts of endotoxin. So this is an important project that I think really touches on a lot of our regulatory activities.

A second project is, again, continuation of work that I started at Children's on the latex allergen Hev b 5. Latex allergy, as I don't have to tell any of you, is an important allergy that seems to effect both children with spinabifida and health care workers worldwide. Hev b 5 is one of now 13 allergens that have been described in latex. It's unusual in that it appears to be important in both populations, both the health care workers and the spinabifida, the children with spinabifida. And we've been working hard to identify the IgE binding sites on Hev b 5.

We've now mutated what we believe to be the IgE binding sites.

We're doing studies collaborating again, with out colleagues in Australia on doing studies both in animals and in cultured human cells to look at the effects of these mutations. And finally, and this is a project that it's sort of hard to believe it just started about 12 months ago because we've really made such exciting advances at this point, we've been building IgE combinatorial libraries in our effort to study immune responses to cockroach allergens and Jonny Finley who is a post doc that just started last year, has really been spearheading that project.

What we've been able to do is we've been able now to construct these IgE combinatorial libraries for only five mls of peripheral blood. Past studies have really required 20, 30, 40 mls of peripheral blood which is certainly obtainable when you're doing studies on adults, but since our interest was looking at cockroach allergy in children, we were limited by that technical barrier and Jonny has now overcome that. He's now constructed two libraries that seem to be functional from five mls of peripheral blood and we have an active protocol to recruit more children from Children's Hospital for this study.

Melissa Patterson has done a great deal of work looking at cockroach allergen extracts in the United States. Again, this was the work that is going to be published in Clinical and Experimental Allergy. And this is really the beginning, as I introduced last year in our effort to standardize cockroach allergy extracts in the United States.

And that's my summary of the site visit. Again, at this point I was going to introduce Dr. Rabin. I apologize but will go on, I think, to the discussion of this.

DR. LEHRER: Are there any questions from the committee members? Yes.

DR. SOTO-AGUILAR: Yes, I have two questions. One regarding the RSV. Since you are involving now yourself into biology and immune response, have you thought of including Esptein-Bar virus which can lead to so many immune responses, so many different types?

DR. SLATER: I'm sorry, have we thought of looking at what?

DR. SOTO-AGUILAR: Of Epstein-Bar virus and -- EBV and what happens with the immune response. As a rheumatologist, I see the most -- our largest variety of immune responses, much as the chronic

fatigue syndrome, I'm talking of monocytosis for a long period of time, all different types of serial responses, IgM combined with different types of IgE, antibody response to the epitopes and what is really happening over time.

That, I think, is a very interesting, very intriguing type of virus and the potential effects on the immune response. That's one question.

The other one pertains to cockroach. Six years ago I presented data showing that Caucasian population responded very differently serologically to the African American population with respect to their IgE responses. They seemed to respond to different epitopes. Have you done that? Are you looking at different type of serobank and see what happens?

DR. SLATER: Well, in response to your first question, thank you for the suggestion about EBV. I will talk to Ron about that and we'll look at that but I appreciate your comments. Certainly EBV is an important virus and we know that it does alter immune responses, so that's a good suggestion.

As far as the heterogeneity of the IgE response to cockroach, that's actually one of the reasons that we're pursuing this project the way we are. You know, I think one of my concerns about

standardizing cockroach allergen is specifically that, that we need to try to do our best to identify the allergens that will lead to safe and effective products in as broad a population as possible and my -- you know, I obviously didn't give you a thorough presentation of the cockroach work but really one of our major objectives is to really look in a more specific and rigorous way at what the epitopes are, what the relevant allergens are and what we need to measure as we go forward with standardizing these two important allergens, but I think your comments are very important and thank you.

DR. BERGER: In a related sort of question to the last point, do you have a way to correlate the things you recover in making a combinatorial library with what's actually displayed on the mast cells in the patient you got the peripheral blood from?

DR. SLATER: Well, I don't have the tools to correlate it now. I think we certainly could build that into the study later. I think that's a good idea. There's no way -- you know, one of the beauties of these libraries is you really -- we use the Pax gene system for drawing the blood. It actually gives us a very nice quick freeze frame of the RNA at that moment. I don't have any way of freeze framing the

mass cell sensitization at that moment as well. But certainly, I think it's something -- I think you're raising a good point. I think once we're able to -- what we're able to identify using the combinatorial library, we probably need to go back and correlate it in vivo.

That's a project, that of necessity, is quite aways down the pike because that would involve introducing product into people. Presumably with basophil histamine release, we could do it in a less than basic way.

DR. BERGER: I think a related question or suggestion might be in a few, you know, representative cases to sort of at the same point in time, compare the same combinatorial library approach on tonsilar cells with peripheral blood taken from the same patient at the same time. So that would, perhaps, give you snapshots comparing what's in the peripheral blood versus what's in a respiratory tract associated lymphoid -- solid lymphoid tissue as an approach towards what is the relationship between peripheral blood and mucosal antibody production.

DR. SLATER: That's actually a terrific suggestion, because we are obtaining the consults and we could easily -- that's actually an outstanding

suggestion, thank you. That's really good.

DR. UMETSU: You mentioned your interest in looking at LPS as an adjuvant in some of these extracts. What is the current data that's collected on allergen extracts with regard to LPS and endotoxin? Do you look at that content in the commercialize extracts?

DR. SLATER: No, we don't look at it routinely. Really, it's not something that is monitored in allergen extracts. So it's actually something that we're looking at and that my predecessor in the lab looked at quite awhile ago, so it's kind of fun because the previous data is from the same laboratory but completely different cast of characters.

DR. UMETSU: But isn't that -- I thought all products that are administered to people are monitored for LPS content. That's not true? Is that just for drugs or intravenous products?

DR. SLATER: Allergen extracts are excluded from that requirement.

DR. LEHRER: Pursuing the LPS issue, I had question; you mentioned that there was a fair amount of variability when you looked at manufacturer to manufacturer. What about with the same manufacturer,

if you look at different lots of the same vaccine or if you look at different samples from the same manufacturer?

DR. SLATER: I think that's a very good question. We haven't done hundreds of lots at this point, so we really can't -- I really can't give you a statistically valid comment on that. I think based on my review of the data, I think the differences between manufacturers are far greater than the variability within a manufacturer. So I think that we certainly do see variability within a manufacturer but it's much less than we see between the manufacturers.

DR. LEHRER: And do you see that one manufacturer may seem to have higher levels of endotoxin within their product line as opposed to other manufacturers or is it just one product in particular?

DR. SLATER: Well, in the studies that were done several years ago, the highest levels were clearly present in the dust mite and house dust extracts with levels in cat as well. We didn't look at pollens this time around. We haven't looked at them yet but we're going to. The -- you know, all of the extracts that we looked at had some level of endotoxin in them, that is the two different species

of dust mite and the cat extracts.

And you know, there were some manufacturers that were higher and some that were lower. And part of the purpose of this project is to try to determine whether the differences is biologically meaningful. It may or may not be, we just don't know.

DR. LEHRER: Actually, that was my last question in terms of real life, and you have no information on that.

DR. SLATER: That's the purpose of the project is to really try to determine whether these differences mean anything. And my guess is they may not. I think it's -- you know, we are not able to make a direct comparison between a product and an identical product that has no endotoxin, it's endotoxin free. We still haven't quite worked that out yet.

The problem is that all of the methods that we've tried to use to remove endotoxin and there are many, also remove allergen. So it's kind of hard to separate them out properly but we're working on that.

DR. LEHRER: Also what I was getting at is the levels of endotoxin that you're detecting in

comparison to levels of endotoxin that have perhaps been shown in other products that cause problems, how do these -- how to your levels relate to those levels?

DR. SLATER: I don't know the other data, that's the problem. I don't really know the other data. I don't think that this is anywhere near the doses that were used in studies long ago looking at the biological effects of endotoxins in humans. These are much lower levels.

DR. UMETSU: How about in terms of the reaction, the LPS content, you're looking at the adjuvenicity of LPS. Could it also be involved in causing immediate reactions when -- on just giving the shots?

DR. SLATER: You know, I don't think that that actually has been -- immediate febrile reactions, is that what you're talking about?

DR. UMETSU: Yeah, exactly, a toxic reaction on giving the shot. Yeah, exactly.

DR. SLATER: I don't know. Again, I think that the doses that are in the allergen extracts are substantially below that threshold but -- well, I know what they are in the ones that we've measured but I -- you know, we don't have broad data.

We don't have any -- I should tell you

that this project did not start out with a clinical problem. In other words, we weren't confronting a problem. We had data that suggested that endotoxin -- data not just from me by any means, data from many sources that suggest that endotoxin can effect the immune system's responses to antigens. And so we wanted to look -- we wanted to investigate this as much as possible, to be diligent about what role in life you play in the allergen extracts.

We still have no evidence that there is a clinical problem with this but we're trying to look at it in as step-wise and organized manner as we can. But we are concerned about that.

DR. LEHRER: Dr. MacDonald?

DR. MacDONALD: Jay, your seminal work with latex allergy alerted at least this nation to not use it any more in many -- I would assume like Hopkins, many institutions are not even using it any more. So my question is, what is it that have been occurring in other countries or have -- you know, is there a necessity to continue work on latex allergies because nobody uses it any more?

DR. SLATER: I actually think that's a terrific question and it's come up in several settings and I think that -- I don't know that answer about

what's happening in other countries. I know that what you're saying is happening in the United States is clearly true. And those of us that see patients are not only aware that we're not using latex gloves any more but we're aware that we're just seeing fewer and fewer new cases.

Certainly, you know, the doctors that take care of spinabifida patients are well aware of this problem and these children are not exposed to latex in the first week of life during their closures any more. And so we're seeing it a lot less. It's decreasing as a clinically significant problem. And so the question arises as to whether continuing to study latex allergens is really worthwhile.

I think we have learned interesting things from the latex allergens that we've studied. I think that, you know, what we learn about tailoring immunomodulatory therapy for these patients, those patients that have latex allergy many of them still have it and it's quite severe. So there is a cohort of individuals out there who are still sick and still are fairly limited in their activities.

As you know, most healthcare workers can get by with relatively easy measures, but a significant number had to quit healthcare in order to

prevent episodes. So I think there's still a cohort of individuals who are sick. I don't know that novel sensitization is necessarily a major issue outside of this country. I suspect that it's not but I really don't know the answer.

But I think that the science is still good. The science is still relevant to other allergic responses and we're going to go forward.

DR. LEHRER: Mr. Hauck?

MR. HAUCK: Just a point of clarification to the panel. Allergenic extracts are exempt from endotoxin testing. One of the problems of testing had been the technical problems with interference with some of the enzymes present in the extracts. So that is one of the reasons it's exempt.

The second thing you should be aware of is that allergen manufacturers must monitor the bioburden of their source materials through to finished product. So although it's not endotoxin level, manufacturers have an idea of the bioburden of the source material and what happens during the processing to assure that that bioburden doesn't get added to. I just wanted to clear that up.

DR. LEHRER: Any comment from the committee members? Any comments from the public?

Thank you very much, Doctor Slater. We now have a break scheduled. We're running ahead of time. So we'll just allot, I believe it's 15 minutes for the break. Please adhere to that so that we can continue in a timely fashion in this review.

(Off the record at 9:28 a.m.)

(On the record at 9:48 a.m.)

DR. LEHRER: Now, let's continue with our meeting. The next presentation will be particulates in allergen extracts and compliance overview. Dr. Slater?

DR. SLATER: Well, thank you. This is the first of two regulatory updates of topics that were discussed last year. And I'm going to give a brief background presentation about particulates in allergen extracts. There's not particularly much new to show here but again, I'm -- you know, with the committee with there being so many new members of the committee I think it's very important to bring people up to date and following my presentation, Teddi Lopez will be giving a compliance overview, an overview of compliance activities in the allergenic manufacturers and included in that she will be touching on compliance issues as relates to particulates in allergen extracts.

Just to give a historical perspective, precipitates or particulates in allergen extracts have, in fact, been recognized for many years. There were early efforts in the 1970's by the allergenic manufacturers to characterize these precipitates in terms of their physical descriptions and in terms of solubility properties and there were also early efforts by the manufacturers to remove the precipitates by instituting manufacturing changes, bulk settling steps and formulation changes using different kinds of extraction fluids.

This is, in fact, a very old problem. And if you go back to the Journal of Immunology from 1923, and look at Professor Coca's -- one of Professor Coca's papers, in which he describes the preparation of fluid extracts and solutions for the use and the diagnosis and treatment of allergies, with notes on the collection of pollens, this is one of the original formulations of Coca's solution. He has a fairly lengthy description of the problems that they encountered with precipitates.

"In most of the extracts and preserved juices, a precipitate forms upon standing. As precipitation continues even after the fresh extract has been filtered, it is necessary to wait until the

precipitation is complete before carrying out further steps in preparation. In the case of some of the vegetables, this precipitation has been found to cause relatively little reduction in the nitrogen content, the protein content of the extract. On the other hand, the precipitate in the extract of meats and fish is doubtless wholly protied. Conceivably some of the exciting agents of the allergy", what we would call allergens, "to the original material are in part or entirely lost by this precipitation", but then he admits, "We have no evidence to offer on this point".

He then talks about the particular method they used to clear these precipitates and I was especially taken by the next comment, "The precipitate that forms in some of the extracts is so voluminous that it is impossible to use the centrifuge for removal. In such a case, a partial separation can usually be effected by the use of a fine mesh towel laid over the sieve. As the precipitate tends to form an impervious mat upon the cloth, it is necessary at intervals to scrape off the collected material with a large spoon".

So this obviously is a problem that goes back a long way. But how did the issue arise for us? The issue arose for us in that between 1999 and the

present, the appearance of precipitates was noted during team biologics inspections of several firms. And the issues -- the areas in which these precipitates were observed by the inspectors were in the bulk containers, the final containers, the retained samples and also in the customer complaint and product return files. In other words, they actually saw precipitates on site but they also saw the paperwork suggesting that physicians were returning these products, were complaining about the products to the manufacturers.

Of the standardized extracts, the only one that really is a major issue is short ragweed for reasons that we can touch on later, and this is an example of a precipitate in a commercial short ragweed extract. This is a relatively small button at the bottom of an otherwise clear solution. This is a somewhat more disturbing one, although I think from a regulatory point of view, they're both quite disturbing.

What is our current knowledge about these precipitates? Well, we have a fairly good idea that the aqueous extracts precipitate more than their glycerinated counterparts. This is not to say that glycerinated extracts don't precipitate. They just

precipitate less often and smaller precipitates.

Aqueous short ragweed extracts commonly precipitate and again, among the standardized extracts it's really the only one that's a major problem. Precipitates are a primary cause of physician complaints, usually about visual appearance, and product returns to the industry. Precipitates do not appear to be caused by microbial contamination and we have extensive data from the manufacturers to support that statement.

And it's pretty clear that the extraction ratio and the concentration of the extract as well as the phenol content may contribution to precipitation. Now, we actually initiated a very small scale study that we've not expanded yet in our laboratory in which we took several precipitated short ragweed extracts, filtered out the precipitate that was actually there and dialyzed the extracts into different modified diluents to try to look at the effects of these different diluents on subsequent precipitation.

Again, the precipitation is an -- as you would expect, it's an ongoing dynamic process where the manufacturers filter out the precipitate which for some extracts they do routinely, the precipitation continues on for quite awhile. And what we were able

to observe and this is an OD in the visible range, looking at the precipitation that occurs in time, is that basically all of our extracts eventually began to precipitate and these are all filter sterilized extracts but all of them eventually begin to precipitate but the one that really was -- and this one here was actually stored at room temperature and that actually, to my surprise, at least, precipitated more rapidly than the others. But among the ones that were stored at refrigerator temperature, the one that was most dramatic was the ones which we added an abnormally high amount of phenol, one percent phenol to the solution. This is actually an observation that some of the manufacturers have made as well.

Now, this isn't to say that the entire problem is phenol, nor is this to say that the entire problem would be solved by glycerin but certainly we have evidence to suggest that the more concentrated one precipitate more. Aqueous ones precipitate more than glycerin and the phenol may be contributing to the precipitation.

Our current regulatory position is that we've told manufacturers that no shipment of final containers exhibiting precipitates should occur. That they need to institute a way to inspect them to make

sure they don't contain precipitates and not to ship them out to their clients. The development -- we want the manufacturers to develop an in-house quality control program to identify and describe the precipitates.

They need to validate any reprocessing procedures performed on precipitated extracts. They need to modify their labeling to address precipitates. They need to submit what's called Biological Product Deviation Reports and you'll hear more about that in a few minutes from Teddi Lopez, on precipitated lots to CEBR and if no approved license supplement is in place for reprocessing or reworking precipitated products, one needs to be submitted.

I just wanted to note that in the CFR there is already the requirement that in the dosage and administration section of the package insert, there be something similar to the following statement "The parenteral drug products should be inspected visually for particulate matter and discoloration whenever the solution and the container permit".

We have recommended several changes to the manufacturers in terms of their package inserts and these are by way of recommendations. We've recommended that the package insert contain a

statement indicating that precipitation occurs. We've also recommended that there be a description of the typical appearance of the precipitate and finally, we've recommended that there be a statement that precipitated extracts should not be used in patients.

So in summary, we know the precipitates occur and probably have always occurred in allergenic extracts. We know that aqueous extracts precipitate more than glycerinated ones. We know that almost all, with the exception of short ragweed, almost all the precipitated extracts are unstandardized. There are still significant knowledge gaps on precipitated extracts. We're collaborating with industry to fill in those knowledge gaps and at this point, we're pursuing what we consider to be a prudent regulatory approach.

Did you want to have questions before Teddi Lopez speaks or do you want to proceed with the next --

DR. LEHRER: Since it's a continuation of the same topic, I suggest that Teddi Lopez present and then we can present the issue of precipitates.

MS. LOPEZ: Good morning, my name is Teddi Lopez. I'm from the Office of Compliance and Biologic Qualities, Division of Case Management. The first

slide here is just the slide of the agenda. It's a very short agenda. First I talk about enforcement actions or the types of tools that we have available to us when we find that a firm is not in compliance with GMPs. I also show a few slides of enforcement actions versus the total number of inspections over the entire industry and of course, include the allergenics.

I'll talk about the Biological Product Deviation Reports and this is a mechanism that the agency can use to monitor what is going on across industries as well as with a particular firm, talk a little bit about recalls, talk about those concerns or items on a 43 or inspection report that might lead the agency to take a regulatory enforcement and finally the last slide -- the last couple of slides will be about forward thinking and I'll talk a little bit more about the precipitates and where we are with that.

Starting with enforcement actions, warning letters, that is the first form of notification that we will send a firm. Basically, it's the notification that says, "We've had an inspection at your facility. We have noted the following deviations. If you don't implement effective and appropriate corrective actions, the agency, without further notice, can take

another action, another stronger action".

And usually those actions fall into two categories, legal actions and administrative actions. For legal actions, we have seizures and injunctions. For administrative actions, we have a license suspension, license revocation or otherwise perhaps known as notice of -- excuse me, Notice of Intent to Revoke and then other.

License suspensions, we don't do those very often but should the agency determine that we have an immediate health hazard situation, we will immediately suspend the license. Notice of intent, basically, again, we say, "We've had a few inspections at your facility. These inspections have been violative. We found repeat deviations. If you don't clean up your act", essentially, "we will revoke your license".

Under other, we have a letter after notice of intent and in that situation a firm is currently under notice of intent. We go back out, do another inspection and while they have made significant improvement, which would tell us that we don't need to move forward in revoking a license, we still do have concerns and so we will send a letter out to that effect.

And then regulatory meeting with the agency in which we will call a firm and say, "You need to meet with us. Please bring, you know, this personnel". We'll tell them who we'd like to see, "And be ready to address certain concerns". And at the meeting, usually the office director is going to be there to relay to the firm our serious concerns.

This slide is just for the enforcement actions for the allergenic product manufacturers over the past several years and basically I'll just note that in '97, '98 and fiscal year 2000 we had more warning letters issued than any other type of regulatory action. In FY 2001 other led the charge, so to speak and they were notice after letters of intent. We do have a couple of firms under notice of intent and a regulatory meeting.

Now, the next three slides basically show the total number of inspections versus the number of enforcement actions, for fiscal year '99, 2000, 2001, for the entire industry and for allergenics, there were eight total inspections and three of those led to an enforcement action. For 2000, there were 12 inspections at allergenic manufacturers, five of which led to an enforcement action, and in 2001 there were 10 inspections, three of which led to an enforcement

action.

Now, the next slide just really talks about where the dividing line is. If an inspection took place in fiscal year 2001, however we took, an action in 2002, we counted that inspection for 2002. Other inspections completed in fiscal year 2002 pending classification or review. Basically, there are three classifications for an inspection; NAI, which is no action indicated, and the agency obviously won't take regulatory action, VAI, voluntary action indicated and again, the agency will not take a regulatory action.

There were some valid observations that we found on a 43. However, they were not significant enough to lead the agency to take a regulatory action. And finally OAI, official action indicated, those are the types of reports that come to the Division of Case Management. We look at the evidence, the inspection report, the firm's response and determine what action we should take.

Now for fiscal year 2002 there have been, let's see, five inspections but thus far we do not have any enforcement actions. A couple of the inspections were classified VAI. At least two inspections are currently under review at the center,

they were OAI and so we're currently reviewing them so I don't know where this will end up. We may reclassify them to VAI or we may opt to take regulatory action.

Biological Product Deviation Reports, the reg became effective May 2000, excuse me, May 2001, and essentially we want to know when a firm has had problems with a lot that is already in distribution. And that's the key phrase there "in distribution". If the lot is still under the firm's control, they do not have to submit a biological product deviation report. But once the lot is no longer in their control, if it's at the user end or at a warehouse that they don't control, we expect to see a Biological Product Deviation Report and the report should contain the lot numbers, the problem identified, an investigation and any corrective actions that were implemented.

And here we just have a quick slide on what the entire non-blood industry looks like for the past few years. The 2001, that black column represents the allergenics and that spike corresponds to the implementation date of the final rule. And most of the reports had to do with precipitation. And let's see, I wanted to go back to a slide. Yeah. In 2002, we have thus far had 192 Biological Product

Deviation Reports for the entire industry. Of the 192, 121 or 63 percent represent the reports for the allergenic manufacturers.

And a further breakdown of that, 12 reports were for labeling, eight reports were for QC and distribution and 100 of the reports were for product specifications, that's 83 percent of that 121. And it's interesting to note that of the 191, were because the product contained precipitate. Now, the agency has indicated that a manufacturer may report -- may combine these reports as long as the meet the 45-day time frame.

That is to say, if you have lot X an you have 13 complaints, you may submit one report and list the 13 complaints or you can submit one report and list various lots. So there's no need to send in one report for each complaint.

And as Dr. Slater mentioned, this issue was discussed in October and we have found that for the most part, firms have implemented interim measures. And for us that basically really means prior to distribution, firms have written SOPs that say, "Take a look at these vials before you distribute them, and if they have precipitation, they're not to be distributed".

Recalls, and they're voluntary on the part of the manufacturer and for allergenics, most of the recalls that have been issued to date relate to labeling. And for the fiscal year 2002, so far there have been nine recalls and most of them had to do with labeling. There were seven that had to do with labeling and usually it was because of an incorrect expiration date. We had one recall that was due to a sterility issue and one recall that was due to QC and distribution. It was an unlicensed product.

Now, the next few slides are really about the types of concerns, issues that would lead the agency to take a regulatory action and this is a compilation of issues that we've seen from 1999 to 2002. Currently, we're not seeing all of these but we thought we'd tell you what the history has been.

Leading off, we have inadequate investigations and corrective and preventive actions. I went back to the previously 43s and inspection reports and just pulled out some of the observations that we've seen that may have led to enforcement action. And I'll just go ahead and read a couple of them.

"Investigation was not conducted to determine the origin and nature of precipitates that

were found in batches of extracts". "Complaint was received for precipitation vials, however the investigation did not include testing of the return or reserve samples and no corrective action was implemented".

Next, we have refiltration, reprocessing and reworking and usually it's the lack of validation of these processes. A firm will go ahead and reprocess a lot that has precipitation and there's no assurance that they haven't determined whether or not this has an adverse impact on the product quality. In one of the examples cited in a 43, there was no data to support reprocessing when certain limits were exceeded. The SOP did not specify the number of times that a lot may be reprocessed and there was no requirement for an investigation.

Container closure, these are container closure integrity issues. We don't see this particular observation as we did in the past. Validation issues, we still continue to see and this is a lack of validation for processes, systems, tests, also failure to qualify equipment. A couple of the observations that we've seen on actions or on 43s that have led to regulatory actions. No data to support the validation of the sanitization cycle for the water

system, cleaning validation for product contact, manufacturing equipment has not been validated, failure to conduct cleaning validation studies for removal of residual protein for equipment.

We also have reserve samples, CFR 211.170 says in part that, "A manufacturer must maintain reserve samples and visually inspect them at least annually to look for visible deterioration". And what we find upon inspections that they may have these samples but they don't look at them on an annual basis. And sometimes the investigator will say, "Well, let's go take a look at them now", and when they do, they'll see vials that have precipitation.

Biological Product Deviation Reporting, this is still an issue. We continue to see this particular observation. So let's see, some of what we see are failure to report shipping of products without an expiration date, failure to report discoloration and precipitation of allergenic extracts. SOP deficiencies, we see this a lot but this goes across industry lines of failure to follow an SOP, failure to have an SOP, of failure to have an adequate SOP.

And then annual review, 211.180E says that you have to take a look at records just to make sure that there's no reason that you need to change certain

specifications. I mean, if you're looking at, you know, certain records, you may determine if there is a trend or a shift and you may need to go back and look at a process or perhaps, revise some specifications.

And as I think I eluded to earlier, we have seen a lot of improvement. We don't see as many issues regarding container closure integrity. The SOPs are getting better. Where there were no SOPs before, there are SOPs now. We find that employees are following the SOPs and that for the most part they are adequate but they still need a little bit of tweaking.

Validation, that is improving as well, including for refiltration. As Dr. Slater mentioned, you know, we expect that this process is validated and that you send in a supplement to the agency. People are now doing the annual reviews and looking at retention samples at least annually for deterioration. BPDR reporting is getting better particularly for precipitates but we see still as an issue when precipitates is not the cause.

And I have one slide here about forward thinking as far as the precipitate issue is concerned. Dr. Slater gave you a pretty good synopsis.

Basically, we will continue to work with the manufacturers with the goal of understanding and preventing. We expect that there should be an interim plan to prevent precipitated vials from being released, a label basically alerting physicians that they shouldn't use vials that are precipitated. Also that these reports may be submitted en masse. Instead of submitting one report for every complaint of precipitation, you can put them together as long as you continue to meet the 45-day time frame.

And here is just some contact information for you. That's it.

DR. LEHRER: Thank you very much, Teddi. The presentation by Dr. Slater and Teddi Lopez is now open for questions. Are there any questions from the committee members? Yeah, Harold.

DR. NELSON: Well, having used these extracts for 30 years and seen precipitates in them and never worried that much about them, I just wonder why all of a sudden in 2001 there was this huge jump in the recalls due to precipitates, number one.

And I wondered what we really knew about these precipitates and wondered about this recommendation that says a statement prescribing extracts, that precipitated extracts should not be

used. What is the new information all of a sudden that brings that to importance?

MS. LOPEZ: Regarding the first question that you had, the spike you say was in recall but it was really in Biological Product Deviation Reports. And one of the reasons why we implemented the new rule is because we found for the non-blood industry, there was a lot of under-reporting. The blood industry, which would be blood banks and places like that, they had like, you know, 20,000 deviation reports. So they were reporting but we found for the non-blood industry, they weren't reporting the way we kind of expected.

Also we found that we didn't put a time frame in the previous reg. We expected a timely response. And we found that it could be three, four, five months. And so we implemented that new rule in 2001 and I think that's probably the reason why you see that spike. We believe that those precipitates had always been there, been in product, been the subject of complaints but the firms hadn't been reporting them to us and it wasn't until 2001 when the rule became effective that we started seeing so many of them.

DR. NELSON: Now, is the difference just in reports or were these previously going out and

being used and now they're being sent back to the manufacturer?

MS. LOPEZ: I think that they had -- I think the problem has always been there. It's just a matter of reporting it to the agency. Before 2001, they probably had just as many and the physicians would receive the product, you know, fill out a complaint, send it back and receive a new lot. And I think the same thing is occurring now, but the only difference was the requirement to report them.

DR. SLATER: Actually, when I presented this information last year in New Orleans to the Academy Immunotherapy Committee, most of the physicians on that committee had not been as observant as you. They didn't know that there were precipitates in the extracts that their staff were administering. So most physicians, most allegerists that I've spoken to have not been aware that this has been a problem since 1923.

That this is something that they were confused by. Now, several of them called me up and said afterwards when they went back and talked to their staff, "Oh, of course, of course there were precipitates". Your question of why is there a recommendation now that precipitating extracts not be

used, is there some new information that we have that suggests that it's somehow more dangerous. And the answer is, no, there is no new information but there's actually no old information either. We don't really know -- we know that allergen extracts are basically safe products when used properly.

We also know that there's a baseline of adverse reaction to precip -- excuse me, that there's a baseline of adverse reactions to the use of allergenic extracts. We don't know what these precipitated extracts might be playing either in the administration of extracts that are sub-potent and then the administration with switching a vial to a new far more potent vial that hasn't precipitated out yet or with adverse events associated with the precipitates. We just don't know.

It's actually -- that was the reason that I said at the end, this is a prudent regulatory policy. It's not one in which we have active information that there's a problem but we are concerned and certainly in the rest of parenteral drugs. You know, there are measures instituted to filter out precipitates if they're are an unavoidable part of the process.

DR. NELSON: Of course, Jay, the raw

material that other drugs are made from though is a little bit different from ground up cockroach and vacuum cleaner sweepings. So is there any data with the recent precipitates that this includes allergenic material or even protein, or is it other substances?

DR. SLATER: Remember the only extract that precipitates that we can actually look at in terms of potency is ragweed and we've looked at several lots of ragweed and we've not found that it actually contains AMBAY 1 (phonetic).

Again the techniques that we're using to look at it might not be the most sensitive techniques but we suspect that at least in ragweed it does not contain allergens. That doesn't necessarily mean that there are no problems associated with it. It's a little bit reassuring. Again, when we're talking with the unstandardized extracts, which are the bulk of the problem, we really are in an area where we're almost completely in the dark in terms of the allergen contribution that might be in the precipitated extracts.

Actually, I didn't mention this in my presentation but one of the things that we discussed in last year's meeting when we discussed this was the possibility of doing a survey to try to identify how

many physicians thought this was a problem and how many had seen reactions associated with this and how many just noticed it.

I actually -- a therapy committee of the Academy was working with me to put together such a survey, such a questionnaire but it actually never ended up getting sent out by the Academy to its membership so we really don't have that information.

DR. LEHRER: Yes, Wes.

DR. BURKS: Do you have any idea why the short ragweed has precipitates, I mean, compared to other extracts that --

DR. SLATER: Well, short ragweeds, again, I'm sort of jumping ahead to something I'm going to say in about two hours, but all of the dust mite extracts and all of the grass pollen extracts are packaged and sold in 50 percent glycerin. A substantial number of short ragweed extracts are aqueous and I think that actually may be the issue.

Now, again, I don't want to sell the idea that glycerin aiding ragweed extracts would make the problem disappear. In fact, I've been told antidotally that it doesn't make the problem disappear in the case of ragweed and I see Peter nodding his head up and down. But you know, I think that at least contributes

to it somewhat but again, I'm not really sure.

But it is a little bit frustrating. I'm glad that the other standardized extracts don't have the problem but I think we have a better handle on the problem in terms of determining what issues there might be in terms of allergen potency if we had precipitation in some of those products.

DR. LEHRER: I wanted to ask the clinicians on this committee, those of you like Hal that have noticed the precipitates over the years, have you noticed any diminished biological activity? I know this is a very crude survey but I'm just curious if you've seen any changes.

DR. NELSON: I don't think there would be any way to be able to comment on that just from antidotal observation.

DR. LEHRER: I guess what I was getting at is I think that if there was a gross change, I would imagine that you picked -- one would pick it up if they, in fact, noticed that precipitates --

DR. NELSON: I think if we got ones that looked like the ones Jay showed in the picture, we probably wouldn't use it. Much more commonly, if you hold it up to the light and shake it, you can see just a tiny bit if precipitate but it's usually very minor

in its amount.

DR. LEHRER: Yes.

DR. BERGER: To the extent to which the precipitates in allergy extracts represent large aggregates of protein, whether that's the antigenic protein or not, it may be useful to look in analogy at the story of immunoglobulin which then became intravenous immunoglobulin. And I think that the analogy I would like to suggest is that because our body has rather sensitive effector mechanisms for aggregated IgG, sets off all sorts of effective mechanisms, therefore, our bodies are very sensitive to macromolecular aggregates in concentrated IgG solutions, even if they're not big enough for our eye to see.

And this problem prevented for 40 years the licensing of gamma globulin for intravenous usage and one of -- and it became clear that one could remove the aggregate, the manufacturer would remove the aggregates but aggregates would reform in the bottle in storage as manifest by reactions in the patients. And eventually the way this problem was solved was primarily by including polyols, which is to say sugars in the final iv-Ig concentrates.

So almost every now licensed iv-Ig

product, I don't have a table right in front of me, but almost every product has some sort of sugar in it which was added in the case of the original circa modified ISG which then there were a lot of studies of that with or without 10 percent maltose made a tremendous difference in the stability of that product. That may be a major effect of glycerine but you may be able to achieve it in other things with five or 10 percent of some other sugar.

DR. LEHRER: Thank you. Dale.

DR. SOTO-AGUILAR: I have one question. Go ahead.

DR. UMETSU: I think that this policy which is called prudent assumes that these precipitates are detrimental to the allergen extract's efficacy but it may, in fact, contain significant amounts of protein, perhaps, denatured protein that simply has precipitated out. And although Mel's point about trying to solubilize it or keep it soluble may be good, it's still possible that even if it's precipitated out, it still is antigenic and therefore, might be still useful and to remove it, may actually be removing significant amounts of antigen that could be beneficial.

So I think it's worthwhile perhaps,

looking at this issue much more closely to see what is, in fact, precipitating out before making a policy that may not be appropriate.

DR. SLATER: Well, I think in a sense, at least with ragweed, we've covered that concern in that the reprocessing protocols require the manufacturers to test the extract after they've processed it to ascertain that they're not losing -- that they're still comparable to the U.S. Reference Standard. But I think the point is well taken.

DR. SOTO-AGUILAR: Jay, my question regards to the rubber stopper. Could the exposure to the rubber have any influence in the production of precipitates and on the other hand, are there going to be any changes regarding the use of rubber stopper for possible latex hypersensitivity?

DR. SLATER: I'm not aware of any way -- that's a good question. I'm not aware of any way in which the rubber stoppers could exacerbate the problem with -- of precipitates or somehow cause the precipitates. I suppose that's a theoretical possibility. Stoppers, whether they contain natural latex rubber or other polymers, contain chemicals in them, although I think it's relatively unlikely that that could be the cause.

The samples that we keep in our lab are not kept in stoppered vials. They're actually kept in other sterile vials with no stoppers, so we certainly see precipitation in stopper-free materials. The second question is, are there moves afoot to --

DR. SOTO-AGUILAR: I remember last year there was a brief discussion about the use of rubber stoppers and the potential for latex hypersensitization among people who may have already become hypersensitive or not. We see so many local reactions. How many of those are really related to the allergen to the glycerine or to the rubber exposure, I wonder?

DR. SLATER: Well, I don't think it's been a problem with allergen extracts. I think -- I'm embarrassed to say I'm not really sure which of the manufacturers, if any, still have natural rubber in their stoppers. Peter, are you aware?

MR. HAUCK: There's at least one, probably two or three.

DR. SLATER: You know, it's a problem that physicians are certainly aware of now. I think the studies that have been done and there have been multiple studies looking at the rubber content, looking at the allergen content or rubber stoppers,

are fairly convincing that this is a very, very, very low dose, it's a very low amount. The studies that I'm thinking of involve measuring measurable latex allergen in fluids simply exposed to the stoppers when the vials are placed on the side.

There have been other studies in which multiple punctures, I think up to 40 or 50 punctures have been performed and again, in those cases, measurable allergen has not been determined. I don't think it's a major problem. The clinical setting in which I suppose it would be a problem is if you're finding reactions to injections of saline or to skin testing with saline but I have not heard of that being a major issue.

DR. LEHRER: One last question, Peter?

MR. HAUCK: This is more of a comment again, we have seen some precipitation problems with standardized Timothy, which is a glycerinated extract, although the amount of precipitation is not nearly as much as aqueous ragweed. And in that we -- and again, it's a minimal amount of data. We haven't seen any change in potency at least by competitive binding assay that was significant.

Secondly, regarding precipitation, one of the major issues deals with the concentration of the

material. If you're purchasing a one to 10 weight volume or even to some extent one to 20 weight volume, that's a very high concentration of protein, a lot of total solids in suspension. What manufacturers see is those are the ones that are most prone to precipitation. If you're purchasing below that concentration even in an aqueous form, you're much less likely to develop that precipitate.

On the other hand, that opens a whole other set of issues regarding stability, but I just thought I'd make that point.

DR. LEHRER: Thank you very much. Now, we will continue with the next presentation. Dr. Slater will be addressing reduction of possible exposure to TSE agents in allergen extracts. Dr. Slater.

DR. SLATER: Thank you, again. Again, this is a -- this is really a review and update of material that was covered at length last year. And I'm going to go through some of that material and then we'll give you some updated information on the transmissible spongiform encephalopathies as they may effect or in essence, don't really effect allergen vaccines any more. And I'm going to give you the punchline in advance, so this is our summary slide for allergenic products.

And the news is basically very good. It was good last year and it's better now. Most allergen extracts are produced without any bovine components; however, mold extracts are stored and propagated in culture media and some of these culture media contain bovine components and in the past, that was of uncertain origin. But again, the punch line is the risks associated with these contaminations are minimal.

And I'm going to now take you through a very abbreviated process which, as I said before, we went through at great length last year to show you what we thought should be done at that point and what has been done since then.

This is just a very selective time line of some of the regulatory activities that we've had. This has been going on for quite awhile as far as the FDA is concerned. In May '91 CBER sent a letter to its manufacturers alerting them to problems of bovine components from certain countries. In December '93, the FDA sent a letter to its manufacturers similarly alerting them. In December '97 was when the USDA expanded its list of banned countries to include all of Europe.

Originally, the problem was in the United

Kingdom but in '97, the data suggested that this was a more widespread issue. In April of 2000, CBER sent another letter to its manufacturers and in May and August of 2000, we sent letters to our allergen manufacturers basically asking them for data. We were asking them for information about their products which in many cases was fairly hard for them to pull together but we were looking for certification data about either the presence or absence of bovine materials in all of their products and certificates or certification that these products were from countries that were not on the USDA list.

I list here in July 2000 there's a TSE advisory committee. In July 2000 the TSE advisory committee met together with the Vaccine Related Products Advisory Committee. That was a fairly important meeting at which some of the principles that we're going to talk about were established.

With the data that we obtained from our manufacturers, we then went through a rather laborious process of risk assessment in which we attempted to quantify or really estimate the risk associated with the injection of these products based on all of the following information. We were concerned about the animal source. If there were bovine components, where

did these cows come from and when did they come from that place?

We know that the appearance of bovine spongiform encephalopathy is not -- was not a problem even in the UK prior to 1980. So we want to know both the time and the place and we wanted to know what tissue was actually used and we'll talk about the different risks associated with different tissues in a moment. We asked for detailed information from the manufacturers as to how these extracts were prepared so that we could make an assessment of whether there were any processing or dilutional issues that might reduce the exposure or unfortunately found in some cases, enhanced the exposure.

There are precipitations for mold proteins that would be expected to precipitate out the infectious agents as well. We wanted to know what typical protein doses were associated with immunotherapy, what kinds of dosing they received and if there were any route-specific risks. The assessment of risk of infectivity of the tissue is based on a fairly contrived high exposure method in which tissue is injected into the brains of calves.

Obviously, we don't give you know, therapy by that route and the immunotherapy given by this

route is associated with a somewhat reduced risk. These are the different categories of tissues ranging for Category I which is considered to be high infectivity. Obviously this is neural tissue. Medium infectivity is some tissue associated with the central nervous system and also lymphatic tissue as well. Low infectivity tissues are listed here and then Category IV are tissues that include -- that are thought to contain no detected infectivity. This includes, by the way skeletal muscle which will play into some of our discussion later on.

There are special categories and these are, by the way, from various advisory committee meetings, that there are special categories that are of concern to us. Glycerol, obviously, is something that on the face of it, would be of concern to us because it's such a prominent component of allergen extract. It turns out that most glycerol in allergen extracts is of plant origin in any case and that minority that is of animal origin is not and has never really been considered to be infectious because of the processing that it goes through.

So glycerol fortunately for us in allergenics is really not an issue. Milk, which is a component of several growth media is also not

considered to be infectious based on a fair amount of accumulated data. Gelatin, which is an additive in several growth media, originally was not considered to be infectious at all and it probably is quite safe, and certainly you'll see some of my calculations later on that suggest that it's quite safe but you should know that the TSE advisory committee now recommends against its parenteral use and that obviously, effects us because these are parenteral products.

So the process that we use to estimate the risk starts with the cows and ends up with the actual doses that are administered to people that are receiving immunotherapy and in this slide, I take you through the first half of that process, going from the cow to the actual growth medium itself and in another slide, I'll take you from the growth medium down to the people.

Again, this is all an effort to estimate the infectivity of the medium here at the bottom in terms of LD50s per ml. We start out with the cows, themselves, the tissue that's used and what the LD50 per gram is. Then we estimate how much gram of this particular tissue is in each cow, how many cows are used in a particular lot of the product. We have to look at the regional risk per cow. Not every cow is

infected, obviously, even from an area that's on the list.

We look at the various process reductions in terms of making the medium. We determine the LD50s per lot and then based on the volume of that lot, the LD50s per ml. Based on our review and based on the data that the manufacturer sent us and also a fair amount of investigation on our parts, we found that some of the media supplements that we had been alerted to turned out not to have any bovine components at all. In other words, the manufacturers had told us that they thought these might be problems but it turned out they didn't.

So Proteose Peptones 2 and 3, Peptamin, Neurospora culture agar and Malt extract broth contained no bovine components and obviously were, therefore, not of any great concern to us. There were three supplements that did contain gelatin but only gelatin, Peptone, Malt extract agar, not broth, and YM Agar and Broth all contained bovine gelatin and we did some analyses based on that.

Fortunately, also many of the supplements, many of them, while they contained bovine component, it turns out it was only milk. And I won't read through these but these supplements again, sort of

dropped off the radar screen because we found that they were only used -- they only used bovine milk as their protein source.

And then there were the media that contained bovine muscle, organs and some of them primarily neural tissue, Polypeptone, Proteose peptone, Proteose peptone 4 and brain heart infusion media which obviously contains a lot of neural tissue. Now, you might wonder why we might be concerned about bovine muscle if bovine skeletal muscle was on the Category IV list of no detected infectivity. That's because if you have pure muscle it has not detected infectivity, but because of slaughtering practices, there certainly is a possibility that it might be contaminated somehow with neural tissue and that has to go into your calculations as well.

Once we have an estimate of what the LD50s per ml are in the medium, we then have to go from the medium to the allergenic product to the patient and again, the molds are growth in the medium. They're all processed, reductions and unfortunately we also process enhancements in the production of these that we have to calculate. Again, the LD50s are all based on cow to cow transmission. We know that cow to human transmission is less efficient and so there are some

relative species barriers that we had to build in.

There are, again, route barriers that I referred to before. We made an estimate of the annual US dose of the products and these are broad estimates, estimated the LD50s per year administered in the United States and then based on that, it's a relatively easy calculation to determine the number of years that we would have to go before we saw a case based on this particular material.

As a result of our analysis of the data the manufacturers sent us, we were concerned about three different scenarios. There are many more than three scenarios that are theoretically possible but these are the scenarios that actually happened in our manufacturers. We had products in which the use of an uncertified medium from Category IV tissue, this is the least infectious tissue, was used in mold propagation process. We had other situations in which there was the use of uncertified media containing gelatin, which is a little more infectious we think than Category IV tissue in mold seed stocks and then finally, we had the use of uncertified media from Category I tissue, this is the brain heart infusion media, in mold seed stock. So we did a detailed analysis of each of these three scenarios.

So let's talk about the first scenario. The first scenario is the use of uncertified media derived from Category IV tissue in mold propagation. And again, I'm not going to take you through each calculation step. We start out with a certain LV50s per gram, go through all of the different processes that we are referred to here, come up with LD50s per year of this particular line of product, so one times 10^7 which relatively easily takes us out to about 18-1/2 million years that we'd have to go before we saw a case from this. This was not a major concern.

We then proceeded to the next scenario, which is the use of uncertified media containing gelatin in mold seed stocks and here the tissue LD50 per gram is somewhat higher. It's 1,000 LD50s per gram. And when we finally go through the calculations for this line of products, the LD50s per year was still pretty low, 4 times 10^4, calculating out to about a 5,000 year interval before we saw a case of exposure in this scenario, also fairly reassuring.

Finally, we were -- we locked at the use of uncertified media from Category I tissue, which is the brain, heart infusion media in mold seed stocks and that calculation, you can see here that the tissue LD50 per gram which for Category IV tissue was .1, for

the gelatin was 1,000, here the LD50s per gram is 1 times 10_7, substantially higher. The process reductions actually were significant though in this case but we still came up with and LD50s per year of 4 times 10^3 or about 500 years between a case based on the administration of the product, also fairly reassuring.

But our feeling was that this was a scenario that we could and should attempt to do something about. So again, just to summarize and then I'll get to what we talked about last year specifically and what we've done in the interim, most allergenic products are produced without any bovine components. The mold extracts are potential or at least a theoretical problem. The risks, it turns out are quite minimal, intervals of 5,000 and 18 million years is certainly pretty minimal by any definition, I would think, and the manufacturers have been directed to assure that all bovine components be certified from approved sources.

But remember the situation that we were dealing with, with that last scenario. This involved mold seed stocks, not mold propagation. And so the question that we asked to the committee last year we set up as follows. In July 2000 the combined

committee, the TSA and Vaccine Related Products Committee suggested that for vaccines the master seed stocks should not be rederived to reduce the likelihood of TSE transmission. In other words, they were dealing with a parallel type of problem but with vaccines.

And the Joint Committee felt that this was the case after agreeing that the risk of TSE transmission was remote and that the risks associated with rederiving the master seed stocks of bacterial vaccines were substantial. So this Joint Committee when confronted with a parallel situation, decided that the risk of TSE transmission was remote; whereas the risk associated with rederiving the seed stocks for these vaccines was real and therefore, they did not recommend rederiving for vaccine stocks, certainly a reasonable conclusion.

But our feeling was in contrast, CBER did not believe that there was any risk to product efficacy or safety associated with rederiving the master stocks of mold strains for allergenic extracts since these are non-standardized extracts to begin with, there is really no defined risk and therefore, we asked the committee and this was the question that we asked in 2001, whether the committee agreed with

CBER that the master stocks of mold strains used for allergenic extract should be rederived to reduce the theoretical possibility of TSE transmission and at the time, the committee agreed with us and felt that this was an action that should be pursued.

In the interim, that action has been pursued and substantial progress has been made in that direction and I can tell you that as of this month, the theoretical concerns regarding TSE and allergen extracts have really for all intents and purposes been resolved. So this was my way of saying that, you know, we really didn't start out with a terribly bad situation last year either. We were confronted with a possibility of a bad situation.

We went through an extensive analysis. The analysis was basically very reassuring with the possible exception of one small part of it which we really, with the committee's help last year, we really were able to take care of during the interim year. So that's the feel good part of the presentation and I think we should all be fairly comfortable that we've done a good job and allergenic products which were safe from this point of view are now even safer.

This is the less feel good part of it and that is that USDA list is and has been a moving

target. And whereas the list as of last year contained these countries in calendar year 2001 five new countries were added to the list. Now, how do you get added to the list? You get added to the list by having evidence of bovine spongiform encephalopathy in native cattle.

Remember this is a list that's maintained by the USDA. This is not an FDA list but it's the list that we use and it's the list that everyone is supposed to use. And of these five countries that have been added, really the one that, for biologics manufacturers is of greatest concern is Japan in which there were three cases in native cattle and it is now on the USDA list. So again, based on a review of the data that we were sent last year, we don't think the Japanese products are really a problem. In other words, we don't think that our manufacturers have been using Japanese products but everybody has to be aware that this is a list that evolves and the manufacturers have the responsibility to continue to assure that their products don't have even potential contamination with BSE.

That list is on the USDA website. The USDA Animal and Plant Health Inspection Service has a website. It is updated all the time and that address