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Allergenic Products Advisory Committee

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A G E N D A

OPEN SESSION

Topic I: Committee Updates/Discussion Points

A G E N D A (cont.)

A G E N D A (cont.)

Topic II: Research Overview

P R O C E E D I N G S

DR. HAMILTON: I'd like to welcome you to the Allergenic Products Advisory Committee of the Center for Biologics Evaluation and Research of the FDA. This morning I'd like to begin by welcoming you, and I would ask that we go around the room and each individual in our group introduce themselves and provide their affiliation. And with the introductions, we'd like to welcome our new members: Dr. Vivian Saper, Dr. Weber, Dr. Riedl, and Dr. Castells.

So I'd like to begin. My name is Robert Hamilton. I'm at Johns Hopkins University in Baltimore. I oversee a diagnostic allergy laboratory and do basic research in the field of allergic disease. Sandra.

MS. FUSCO-WALKER: Good morning. I'm Sandra Fusco-Walker. I'm with the Allergy and Asthma Network, Mothers of Asthmatics, and I'm the Director of Patient Advocacy.

DR. COX: I'm Linda Cox. I'm a practicing allergist in Fort Lauderdale.

DR. GRANT: Andrew Grant, University of Texas

Medical Branch in Galveston. I'm been teaching in this field for just about 40 years now and have been running a training program.

DR. WEBER: Richard Weber. I'm at the National Jewish Health in Denver and the University of Colorado.

DR. SAPER: Okay, obviously I'm new. I'm Vivian Saper, and I've had an appointment at Sanford University since residency. I am Board in allergy, asthma, immunology, pediatric rheumatology, and pediatrics. I see patients. I have experience with subspecialty residency training programs, and I am also medical director of an allergy diagnostic company and run their clinical reference lab.

DR. RIEDL: I'm Marc Riedl. I'm at UCLA, the David Geffen School of Medicine where I'm the head of the section of clinical immunology and allergy in the Department of Medicine, and I'm also on the faculty in the Clinical Pharmacology Department at UCLA.

DR. MARTIN: I'm Bryan Martin. I'm from The Ohio State University, and I'm the Program Director in allergy and immunology there and the associate dean for

graduate medical education.

DR. PLUNKETT: I'm Greg Plunkett. I'm the industry representative. I work for ALK-Abello U.S. and work in our allergy research laboratory.

DR. BAYLOR: I'm Norman Baylor, the Director of the Office of Vaccines Research and Review at FDA, CBER.

DR. SLATER: I'm Jay Slater. I'm the Director at the Division of Bacterial, Parasitic, and Allergenic Product in the Office of Vaccines.

DR. RABIN: Ronald Rabin, Chief of the Laboratory of Immunobiochemisty, which is the laboratory that regulates biologic allergenics.

DR. SELF: Steve Self, Fred Hutchinson Cancer Research Center in the University of Washington; biostatistician by training and codirect a division in vaccines and infectious disease.

DR. CASTELLS: Mariana Castells. I'm at the Brigham and Women's Hospital in Boston. I'm the Director of the training program for allergy and clinical immunology, and I'm the Director of the Desensitization Program.

DR. NELSON: Mike Nelson, Chief of Allergy Immunology at Walter Reed Army Medical Center and National Naval Medical Center and training program director, and we host the United States Army's Centralized Allergenic Extract Lab that provides diagnostic and treatment of materials for a large portion of the DoD and VA.

DR. DAPOLITO: Gail Dapolito, the Designated Federal Official in the Division of Scientific Advisors and Consultants, CBER, FDA.

DR. HAMILTON: Thank you. So, Gail, would you like to open with initial statement please.

DR. DAPOLITO: Thank you. The Food and Drug Administration convenes the May 12, 2011, meeting of the Allergenic Product Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the except of the industry representative, all participants of the Committee are special Government employees or regular Federal employees from other agencies and are subject to the Federal conflict of interest laws and regulations.

The following information on the status of

this Advisory Committee compliance with Federal ethics and conflict of interest laws including but not limited to 18 U.S.C. Sections 208 and 712 of the Federal Food Drug and Cosmetic Act are being provided to participants at this meeting and to the public.

FDA has determined that all members of this Advisory Committee are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress authorized FDA to grant waivers to special government employees and regular Government employees who have financial conflicts when it is determined that the agency's need for a particular individual service outweighs his or her potential financial conflict of interest.

Under 712 of the Food Drug and Cosmetic Act, Congress authorized FDA to grant waivers to special Government employees and regular Government employees with potential financial conflicts when necessary to afford the Committee their essential expertise.

Related to the discussion of this meeting, members and consultants of the Committee were screened for potential financial conflict of interest of their

own as well as those imputed to them including those of their spouses or minor children and for the purposes of 18 U.S.C. 208 their employers. These interests may include investments, consulting, expert witness testimony, contracts and grants, creative, teaching, speaking, writing, patents and royalties, and also primary employment.

For Topic I, the Committee will hear updates on the following: ELISA replacement of radial immunodiffusion assay for standardization of cat and ragweed allergen extracts; statistical requirements for Phase III clinical trials results to consider for BLA approval; and environment exposure chambers for Phase III study. These updates and discussion topics are particular matter of general applicability.

The Committee will also hear an update of the ISO 17025 accreditation process for CBER's intramural research laboratories. This update is a nonparticular matter and presents no actual or appearance of a conflict of interest.

For Topic II, the Committee will hear an overview of the research programs in the Division of

Bacterial, Parasitic and Allergenic Products, Office of Vaccines Research and Review. This is a nonparticular matter and presents no actual or appearance of a conflict of interest.

Based on the agenda and all financial interests reported by members and consultants, no waivers were issued under 18 U.S.C. 208(b)(3) and 712 of the Food Drug and Cosmetic Act.

Dr. Greg Plunkett is serving as the industry representative acting on behalf of all related industry and is employed by ALK-Abello. Industry representatives are not special Government employees and do not vote. This conflict of interest statement will be available for review at the registration table. We'd like to remind members, consultants, and participants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the Committee of any financial

interest that you may have with any affect firms, their products, and if know, their direct competitors.

Thank you. Dr. Hamilton.

DR. HAMILTON: Thank you, Gail. I'd like at this time with great pleasure to invite Dr. Karen Midthun up to the podium to provide remarks and presentations related to those members of our Committee that are actually going off the Committee this year. Dr. Midthun.

DR. MIDTHUN: Thank you so much, and it's a real pleasure to be here this morning and also to really thank all of you for what you for advisory committee. I know you invest a lot of time and effort, and we very much value the expertise and the very important advice that you give to us. I would very much like to thank in particular those members who are rotating off the Committee. I know that during your tenure you've made very important contributions as we have sought input on advice regarding ragweed and cat allergen extracts also advice regarding our efforts to try to complete our reclassification of some allergenic products and also on structured products labeling among

many. Those are just a few highlights that I that you have provided very important feedback to us on.

The three individuals who are rotating off are Dr. Cox, Dr. Grant, and Dr. Plunkett, and I would like to invite you individually to come up, and I think we will have a photo opportunity. So, Dr. Cox, you want to come up first. I think we're supposed to go over there in front of the screen.

DR. COX: Thank you for this honor, and it's been a real pleasure working with the Committee, and I'd like to continue in any way to offer my services. We've got a lot to learn about this particular part of our specialty.

(Pause for photo opportunity)

(Applause)

DR. MIDTHUN: And next I'd like to invite Dr. Grant to come up to the podium.

DR. GRANT: It's been a genuine pleasure to serve and to see the great expertise in the staff and the success that this Committee has had in moving things forward to improve the health of allergy suffers.

(Pause for photo opportunity)

(Applause)

DR. MIDTHUN: And then I'd like to invite Dr. Plunkett to the podium.

DR. PLUNKETT: Well, I would like to thank on behalf of the Allergen Product Manufacturers' Association, the science officer of which I am, gets the privilege of attending this meeting, and it's been an honor.

(Pause for photo opportunity)

(Applause)

DR. HAMILTON: Thank you, Dr. Midthun. So we're now moving into the Topic I of the Committee, Updates and Discussion Points. And I'd like to introduce Dr. Ronald Rabin, will give his overview of the Laboratory of Immunobiology area with regard to the structure and activities of his laboratory.

DR. RABIN: Good morning. I want to thank everyone for being here this morning. It's a pleasure to present all of the presentations we're going to have this morning starting with the overview of the lab.

The Laboratory of Immunobiochemisty is the

laboratory that is responsible for regulation of biologics that pertain to the treatment of allergic diseases with the Center for Biologics Evaluation and Research. As you can see, I'm the Chief of the Lab. Jay Slater is the Supervisory Medical Officer. We have a number of visiting associates who are full-time equivalents who do regulatory and review work as well as participate in the research program. Sandra Menzies is a Consumer Safety Officer, and you will be hearing from her today. Katia Dobrovolskaia, Mona Febus, Cherry Valerio, and Aaron Chen are biologists who are in the lab who do the real work of protocol review and lab release testing.

In addition, the individuals listed below Giulia Fabozzi is a postdoc in the lab, and then the others below her are post baccalaureate research assistants all except for Susan Huynh really only participate in the research part of the program. Susan does participate in the ISO 17025 accreditation program that you'll be hearing about today.

LIB, the Laboratory of Immunobiochemisty, is one of the laboratories in the Division of Bacterial,

Parasitic and Allergenic Products which Jay Slater has recently been appointed the director and Dr. Drusilla Burns is the acting deputy director. Jennifer Bridgewater and Tina Roecklein work very hard with regard to regulatory policy and coordination of regulation within the Division.

The LIB and the Division works hand in hand with the Division of Vaccine and Related Products Applications. It is DVRPA with whom manufacturers, sponsors, and investigators chiefly and primarily work with, and DVRPA is directed by Dr. Wellington Sun, and the Chief of the Regulatory Review Branch Section 1 is Paul Richman. And Dr. Richman is the member of DVRPA with whom our laboratory primarily coordinates its research efforts -- part of the regulatory efforts. Excuse me. In addition, we work closely with Captain Julienne Vaillancourt, CDR Colleen Sweeney, Dr. Nicolette Devore, and LT Elizabeth Valenti.

We have dual responsibilities as you've heard me allude to. We do regulatory review and then research. As far as our routine regulatory responsibilities, they include such things a lot

release in which last year we reviewed 408 protocols; distribution of reference reagents, over 4,600 vials and 110 shipments; and maintenance of our reference reagents through semiannual check. Then we necessary, replace the reference reagents.

Just to give you an idea of the tracking, these are the list of the protocols that are submitted to LIB over the past eight or nine years, so as you can see, it runs around 400 a year give or take. And the number of shipments and vials of reference reagents per year is also relatively steady around 110 or so. There are some leaner years and some fatter years as you can see.

We do replace our reference reagents as necessary obviously, and we have done so. Within the past year, we've replace an extract for house dust mite, the E10-Dp; a cat pelt extract; and reference reagent for ragweed. We've also replaced some sera. The sera that we use for both house dust mite species, cat, and Bermuda grass. We will have to replace more sera for the house dust mite and some more grass sera upcoming in this year.

We manage this inventory of reference reagents through semiannual reference checks. We estimate the replacement dates based on expiring consumption. We monitor manufacturers' requests, and I want to take a moment on the record to thank the manufacturers. We've asked them to submit their yearly request up front to help us monitor the inventory and anticipate replacements, and they've done so, and this has I think worked out well, helped us managed the program, and helped them get what they need in order for appropriate lot release.

And then, of course, we do distribute some of these reference reagents for research purposes, but we limit it carefully so as not to impinge upon the lot release program.

Our review responsibilities are that we review investigational new drug applications. These are broadly divided into two groups: Those that sponsor originated in which the goal is licensure and marketing and investigator originated in which an investigator wishes to use an extract for a purpose other than license such as a bronchial challenge or mechanistic

studies.

We also, of course, handle any relevant biologic license applications, initial licenses, supplements, and annual reports; and we consult for other centers, most commonly our colleagues in the Center for Drugs, who handle allergenic drugs, and occasionally those in the Center for Devices.

And that's it for this part of the presentation. Are there any questions from the Committee?

DR. HAMILTON: Any questions?

MR. COOK: Ron, maybe I don't understand. It's on slide 8 of 12, Reference Distribution. You said the numbers were stable, but the vial numbers look like they're gone up almost double, 4,600. Couple of more slides.

DR. RABIN: Let me. I guess I can do that.

DR. COX: There.

DR. RABIN: Whoa. Yes.

DR. COX: Is that?

DR. RABIN: Yes, you're right.

DR. COX: What does that mean?

DR. RABIN: It means we've been working. It means my group has been worker very harder than I actually have appreciated I think. We've had a lot of replacement, and what actually happened I think that this also reflects our request for upfront -- that we ask people to do some upfront stuff, so what they ended up doing was we had a lot of vials released -- because this calendar year, so we have a lot of vials that were released toward the very end of the fiscal year toward the end of the summer of 2010. And then at the beginning of the fiscal year 2011 in the fall, then the manufacturers told us their yearly needs. So I think that that's where this hump occurred. Sir?

DR. GRANT: You've told us what reagents are being replaced. Could you give us some idea of who many different allergens that you have standards for at this point that you can provide to industry?

DR. RABIN: Yes. A slide in the ELISA versus RID talk will have the complete list, but roughly we manage -- there are 19 standardized extracts. A number of those are venom extracts, which we don't test protocol release for those. So the rest are we have

two we cover for cat, ragweed, a number of grasses and the house dust mites, and you'll got the list in your slide set there. There are a number of grasses. I don't have them memorized. Any other?

DR. HAMILTON: Ron, you've given us a very nice overview of the regulatory aspects of your laboratory. Could you just briefly mention the research side of your lab since approximately 50 percent of your time is spent in research as well?

DR. RABIN: Sure, I'd be pleased. I'll just mention for Dr. Slater very briefly that his research program addresses directly standardization of allergen extracts and in particular he's focusing right now on cockroach extract and determining whether or not there are specific allergens by which cockroach extracts can be characterized and standardized, and I won't speak anymore for that.

My laboratory is interested in the relationship between respiratory viruses and asthma, both of which are strongly associated with the prevalence and the severity of asthmatic exacerbations particularly in allergic individuals. We've mostly

focused on respiratory syncytial virus, and although we started looking at the adaptive response, we've really been focusing much more on the innate response of late.

In particular, we're very interested in the responses of type I and type III interferons to respiratory viruses. And to that end, we've focused even narrowly, if you will, on the fact that there are a number of species of type I interferons all of which act through the same receptor, but some of which at least do appear to some unique biologic effects. So we are taking a two-pronged approach. We have developed an assay to distinguish amongst all the 12 highly identical subtypes of human type I interferon as well as interferon beta and all three different species of interferon lambda so we can look at different expression patterns of these type I interferons in response to viruses.

And then we also have some studies to look at the downstream effects, any unique biological effects of the different subtypes of interferon alpha versus interferon beta on gene expression and on modulation of the adaptive response.

DR. HAMILTON: Thank you. That's wonderful. Any other questions?

(Pause)

DR. HAMILTON: Thank you very much, Ron. Appreciate it very much. Next we'll ask Sandra Menzies to come up and give us an overview of the ISO 17025 Accreditation Program. Sandra.

MS. MENZIES: Good morning. Today I will present a brief history of the environment which led FDA to decide to seek accreditation for its official testing activities, the accreditation process, and an overview of the Laboratory of Immunobiochemisty's efforts to obtain ISO 17025 accreditation.

There are two well-know, pivotal court cases that demonstrate the background of expert testimony in the United States. The first case, *Frye v. The United States*, a witness was considered an expert if that person was accepted as an expert by the scientific community. The requirements for being a scientific expert and providing evidence were not as high as they are today, and during this time, as some of you might know, the Government's word was considered reliable

without evidence.

The other case, *Daubert v. Merrill Dow Pharmaceuticals* concluded that expert testimony is based on the Federal Rules of Evidence. The Federal Rules of Evidence state that testimony is based on scientific evidence and the evidence is relevant only to the case being considered.

Around the same time, Frederic Whitehurst, a chemist with the FBI, reported under the Whistleblower Act that the FBI provided unreliable evidence in high-profile cases such as the O.J. Simpson murder trial and the World Trade Center bombing.

As a follow-up to Dr. Whitehurst's reports, the Office of Inspector General evaluated 51 of the identified cases and concluded that there were several inadequacies in FBI's procedures. The FBI consented among other things to becoming accredited and to undergoing routine external review.

Consequently, the FDA's Senior Science Council assessed the agency's need for a laboratory accreditation and proposed that the FDA centers and ORA independently pursue accreditation of their official

testing activities. FDA's Leadership Council and the Commissioner endorsed this proposal.

So what is accreditation? Accreditation is the process by which an organization is evaluated to ensure that they meet certain requirement by an accreditation body. The evaluation is performed by inspectors who are experts in the fields in which the organization is seeking accreditation, and accreditation bodies undergo international conformity assessments based on ISO 17011 to ensure that accreditations are equivalent irrespective of the accreditation body used.

Laboratory accreditation is one type of accreditation and provides a formal recognition that a testing laboratory is competent and credible and that the test they produce are accurate, reproducible and traceable. There are several organizations that provide standards which an organization can become accredited to. Examples of these different organizations are ASTM, the American National Standards Institute, and the International Organization for Standards.

Of these organizations, CBER selected a standard developed by the International Organization for Standards. This is commonly called ISO. ISO is not an acronym but is based on the Greek word isos meaning equal. ISO has been around for 65 years for the purpose of standardizing international activities. It is a nongovernmental organization which has a process of identifying the global need for a standard then facilitates the development and approval of that standard. At the end of last year, ISO had issued over 18,000 standards. Of these, CBER selected ISO 17025 as the foundation of its official testing activities.

ISO 17025 is named "General Requirement for the confidence of testing and calibration laboratories." This ISO standard was formally called Guide 25 under the same name. The standard ensure competency of testing laboratories through two major components: Management and technical factors.

The foundation of a laboratory qualify system is its management. These elements may be will defined and maintained to ensure a strong laboratory quality system. For example, management reviews the laboratory

quality system at least annually to evaluate the goals of the laboratory quality system. During this review, management examines any finding resulting from internal audits and looks at the other components listed here to ensure that the ongoing development of the laboratory quality system meets the needs of the organization.

Management also ensures that test results are accurate, reliable by using a lifecycle approach within the laboratory quality system. This approach ensures that test methods are appropriate for the work being performed, that the samples are handled in a manner to maintain their integrity throughout their testing, and that test results are reported accurately.

Finally, management ensures test results by developing a laboratory quality system that includes technical elements used by the laboratory to perform a test method. Technical components provide the foundation by which testing is performed such as environmental controls, ordering of services and supplies, ensuring that equipment functions as expected, and personnel are competent.

Since FDA recommended that CBER become

accredited to ISO 17025 in November of 2001, CBER reorganized their lot release program and established a division of products quality which became accredited to ISO 17025 in October of last year. During this time, CBER determined that allergenic lot release testing would remain within the Laboratory of Immunobiochemisty, and LIB initiated the development of a laboratory quality system. LIB is actively working toward the goal of undergoing assessment against ISO 17025.

As shown earlier in Dr. Rabin's presentation, the laboratory's personnel are presented in this organizational chart based on their roles within the laboratory quality system. As shown, the lab chief is in charge of the laboratory, and serving under him is Cherry Valerio as the operations manager, and I am the quality manager. As you can see, the quality function is independent of the operations function.

LIB anticipates accrediting the confirmatory lot release tests, the computational ELISA, and then depending on the status of the development either the radial immunodiffusion assay or the Sandwich ELISA.

LIB has developed and issued over 63 documents describing different aspects of the quality system. In addition, LIB has initiated maintenance contracts for pipettes and balances and completed the method validation of the ragweed RID. LIB is still in the process of documenting qualification of personnel within the laboratory quality system database and qualifying supporting equipment.

In the first quarter of this year, LIB underwent an internal audit. The internal audit focused on the management of the laboratory quality system, and several minor findings were identified. These findings are typical for a new laboratory quality system being developed.

In summary, LIB continues to develop a laboratory quality system that is accreditable to ISO 17025. Our future goals consist of completing the development of the laboratory quality system, undergoing an internal audit of all components of ISO 17025, and being assessed against the laboratory quality system and ISO 17025 by an accreditation body. With this said, a laboratory quality system will

provide management with a mechanism to ensure that results produced by LIB are accurate, reproducible, and traceable. Thank you.

DR. HAMILTON: Thank you, Sandra. Questions? I'd like to begin by asking you ASTM is one of the three organizations. ISO was the one that your group selected, but ASTM allows manufacturers to actually use a method that's validated whereas ISO really is an internal quality assurance for the laboratory per se. So is there any plan or thought to extend some of the assays that you've described to the ASTM standard system as well after you've finished ISO validation of the laboratory?

MS. MENZIES: At this time, I do not know of any process for transferring and working with ASTM to build our test methods within their systems.

DR. HAMILTON: Okay. Good. That may be something we can broach a little later because we've just been through an ASTM validation for an assay for Hev b 1, 3, 5, and 6, which are for allergens in latex, and it's a very lengthy process but involves the manufacturers, and the actual users of the assay is

based on the rubber manufacturers. So it allows them now to run an assay that actually they know is validated and is recognized by a known national body whereas the ISO is a wonderful -- this is a wonderful program in terms of validating the system, the laboratory. It doesn't allow the users, or the manufacturers in this case, to actually have a validated assay they can adopt.

MS. MENZIES: Yes.

DR. HAMILTON: Thank you, Sandra.

MS. MENZIES: Thank you.

DR. HAMILTON: Any questions please? Greg?

DR. PLUNKETT: I was wondering if the validation protocols that you're using like, for instance, the cat RID, are those available to the public to see?

MS. MENZIES: Yes. We have an open system. You would just have to request it.

DR. PLUNKETT: Thank you.

DR. HAMILTON: Sandra, could I ask, you're still in the process of being ISO credentialed, right?

MS. MENZIES: Yes. We are.

DR. HAMILTON: And what is the final step and --

MS. MENZIES: The final step would actually be undergoing an accreditation by an outside accrediting body. The other organization within CBER that went under accreditation was actually accredited by a group called A2LA, and they'd come in -- they provide experts in whatever that you are being accredited against as the type of test. So for ours, it'll be ELISA or RID, and then they look at the test and see do you have the quality system built to support those tests to ensure that the results that you obtain are reliable, traceable, and accurate.

DR. HAMILTON: And you anticipate this outside organization doing this review at some point in the future or?

MS. MENZIES: We're hoping within the next few years.

DR. HAMILTON: Excellent. Great. Thank you very much.

MS. MENZIES: Thank you.

DR. HAMILTON: Any questions? Right here.

Oh, I'm sorry. Michael.

DR. NELSON: Before you leave --

MS. MENZIES: Oh, I'm sorry.

DR. NELSON: -- thank you -- I have a quick related question to that one itself. Thank you for that outstanding introduction of what the process was because it certainly was a black box to me. How satisfied is the organization or the lab with respect to their participation and the timeline in achieving this accreditation? And typically how long does it take once a laboratory commits to undergoing an ISO accreditation from start to finish?

MS. MENZIES: I'd like to reiterate to make sure I understand your question correctly. You're asking about the actual process if a group decided to undergo seeking accreditation how long could it potentially take them. And it really depends on the amount of resources that are available to be able to do this. The Division of Product Quality from the time they started to the time they became accredited I believe was three years. So -- yes, got confirmation. It was three years so --

DR. NELSON: And the big part is the lab satisfied with their current progress in working toward the (inaudible) date?

MS. MENZIES: I'm very pleased with how quickly we have moved. Within the last year and a half, we have really developed a lot of document and actually transitioned the working of individuals to be from a research environment into a quality system environment, and it has been very encouraging.

DR. NELSON: Thank you.

DR. HAMILTON: Dr. Grant.

DR. GRANT: Well, I was intrigued by what you said, Dr. Hamilton, about the differences among the three accreditation agencies, and I'm wondering if there is some need to discuss the value of perhaps going with ASTM because it seems to be the one that many manufacturers used. So might this make the FDA in compliance with the standards that industry is trying to set?

I'm totally naïve of this process, but I was intrigued by that comment that you made.

DR. HAMILTON: My understanding is that the

ISO really is a validation of the laboratory quality assurance program, and it's really for the laboratory internal quality assurance to give confidence to the users.

I was hoping that eventually that these methods might be also applied or submitted to the ASTM as independent methods that could be validated through their system so that maybe manufacturers -- now it may not be necessary -- and actually we'll hear from Dr. Rabin and Dr. Slater whether in fact they feel that this is a necessary step or whether the assays are just so validated as they currently are that it's unnecessary to do that. Dr. Slater.

DR. SLATER: Sure. On a couple of points. One is in terms or your question about our progress in terms of ISO. It seems to me there are two factors in terms of how quickly one can proceed. One is resources that are made available to the cause, and as you can imagine, this is a very big process. And the other is, of course, how far you are toward it when you started. There are surprises in this process that happen, and I think when the people that were involved in LIB's

accreditation sort of started this process I don't think they anticipated the bumps in the road that came. In fact the resources that have been made available have been very solid and very consistent over the years, but I think we've made very, very good progress, but it's been a lot of work and a lot of handling for unexpected bumps.

In terms of the value of ASTM certification of the assays, I think that's a very interesting question that, to be candid, I hadn't thought of before six minutes ago when you raised it. It doesn't really speak to the relationship that we've had with the manufacturers in which we've sort of developed the assays, and then the manufacturers can adopt our assays wholesale, which they often do, or adapt them to their own uses and then demonstrate to us that they're measuring equivalent parameters.

It's not clear to me, again just in the first 10 minutes of discussion, that that necessarily would be a valuable course of action since the manufacturers would always have options and perhaps even an interest in developing their own approaches to the assays. So

there are a lot of factors there that might make ASTM less valuable than it would seem up front, but it's certainly is something that we could discuss both internally and with the manufacturers in a few months.

DR. HAMILTON: Essentially, the FDA has done what the ASTM process actually does, which is to validate all the various aspects of the performance of the assays. So you're providing the data which ASTM would have generated. The only benefit is it's a round robin system within the manufacturers; whereas, you're developing a system, and they are trying to maybe replicate it.

DR. SLATER: At the moment, I think we need to finish the ISO before we proceed to anything else.

DR. HAMILTON: Dr. Castells, did you have a question?

DR. CASTELLS: No, no. I'm fine. Thank you.

DR. HAMILTON: Okay.

DR. CASTELLS: Well, I mean I was going to say that I saw a lot of this -- in terms of the allergens, I haven't heard anything about allergens that pertains to drugs, so I don't know if there was any laboratory

that developing anything like penicillin or anything. And I see the cat and all those being standardized, and I don't know if we have anything for drug-adverse reactions.

DR. HAMILTON: That falls underneath another purview doesn't it? Yes. Ron, can you speak to this issue?

DR. RABIN: Yes. I think that would be under Center for Drugs. We certainly don't handle as far as any reference reagents. We don't deal with that per se.

DR. CASTELLS: Thank you.

DR. HAMILTON: Good. So if there are no questions, let's move on. Dr. Rabin will now give an overview of the transition of the ELISA replacement of the radial immunodiffusion assay for the potency assessment of cat and ragweed pollen allergen extracts.

DR. RABIN: Before I begin, I did want to address because I did want to really speak to the hard work that the laboratory has been doing with regard to the ISO 17025 certification. It's a remarkable amount of work, and I also wanted to complement Ms. Menzies in

particular because she's really directing this and is invaluable in this.

And there's no question -- and Jay alluded to it in a tactful manner of bumps on the road, but it is making us a better reference reagent lab. We're not always pleased to encounter these problems, but we're pleased to solve them, and I think it's made us a better lab.

Allergen standardization according to 21 C.F.R. 680.3 refers to establishing a United States standard and establishing a testing procedure. Manufacturers may use the established procedure, or they can develop equivalent procedures which they might choose to use, which I think addresses sort of some of the issues regarding the harmonization and ASTM that Dr. Hamilton raised.

These are the standardized products currently controlled for potency and stability by the LIB: Two house dust mites extracts, the short ragweed pollen, cat hair and cat pelt, a number of the venoms, and a number of grasses. The unitage varies according to the extract. For venom, it's simply microgram of protein

based on the activity of the allergenic enzymes. For ragweed, it's units Amb a 1/ml, Amb a 1 being the major allergen of short ragweed. For mite, it's allergenic unit; it's common grass, it's biologic allergenic units/ml, which is based on the correlation of skin testing to an *in vitro* assay.

The skin testing is called the ID_{50}EAL testing, the interdermal dilution for 50 mm sum of erythema to determine the bioequivalent allergen units. And what's done is a cohort of highly allergic subjects are obtained, recruited; the allergen is diluted with serial 3-fold dilutions, and the dilution is established at which at which the sum of the erythema is 50 mm, and that's referred to as the D_{50}.

This is sort of graphic illustration of this. These first subjects would just undergo the puncture test to determine that they are highly allergic, and then the quantitative interdermal testing with the serial 3-fold dilutions, the wheal and erythema size, and the sum of erythema size is calculated until you get to the 50 mm.

This is sort of the standardized -- the curve

that's developed, and you could see that you have on the X-axis the serial 3-fold dilution, on the Y-axis the sum of the erythema.

Obviously, for lot release, we can't do this kind of testing on a regular basis, so we have surrogate assays. And for the house dust mites, we measure protein, and we have a completion ELISA using human serum, IgE from pooled human sera. It's the same thing for grasses as well although an IEF is also used, and for *Hymenoptera* it is, again, the major allergens. And then cat pelt and cat hair and short ragweed we do by according to the major allergens, which is Fel d 1 and Amb a 1, respectively. And these are done currently using a radial immunodiffision assay.

So what is the radial immunodiffusion? It is a procedure in which antibodies specific to the major allergen in this case are added to agar. The agar is solidified on a glass slide. Holes are punched into it. Equal amounts of antigens are added to wells. It's humidified to allow the antigen to diffuse into the agar and complex with the antibody, and then those complexes are precipitated after immersion in acetic

acid, and the ring of that precipitate is measured.

Just to give you sort of a picture -- Do I have a pointer on the scale?

(Pause)

DR. RABIN: Just to show you graphically. I don't know if you can see this from the back of the room, but these are the glass slides in which the agarose is drying on a level table. The slides are developed in the acetic acid, and you may be able to see the rings precipitating out. This is the reader upon which the slides are placed. This is Ms. Valerio reading one of the slides. And really, all this is to illustrate how laborious this task is. These are the precipitated ring, and those two vertical lines are the lines that are put around the diameter, the calibrators, to actually measure the ring.

The point that I wish to make here is you could see that it could be rather -- you could see some variability that individuals might have in reading these rings. Do you put those lines exact on the outside? On the inside? In the middle? Where is exactly correct? It's not an easy process, and it is

not a quick process, but eventually, a standardized curve comes from it upon which the unknowns are then plotted against it, and that's how the quantitative value is determined.

As far as values that pass for lot release, as far as ragweed is concerned, there are no limits or target range. The vial is simply labeled "units of Amb a 1/ml." As far as cat is concerned, the potency is considered 5,000 BAU/ml if it the amount of Fel d 1 units/mL ranges anywhere between 5 and 9.5. And then if they range between 10 and 19.9, the extract is considered to have 10,000 BAU/ml.

So what might be an alternative and a better way to do this would be the enzyme linked immunosorbent assay or ELISA. I think that everyone in this audience is fairly familiar with an ELISA. They have a revealing step in which the enzymes couple to a revealing antibody and converts the substrates into a detectable and quantifiable signal, which is usually colormetric; it could be fluorescent; it could luminescent.

I think that you all know the potential

advantages of an ELISA. They're much less time consuming; they're much easier to set up; automated readers; less reagents, and so on.

And again, the method by which a Sandwich ELISA works in terms of a capture antibody, a detection antibody, and then generally some sort of enzyme coupled revealing antibody, or it could be a biocanvadent system that basically gives you your color.

We decided to pursue development of Sandwich ELISAs for measuring Fel d 1 and Amb a 1 and discussed this at the last APAC meeting. And with encouragement of the committee, we moved forward on the project, and what we ended up doing was we chose the single chain variable fragments, the scFv's that were developed the lab by Jay Slater and Nicolette Devore and recently published in the *Annals of Allergy, Asthma and Immunology*. And what we did was we used any of those antibodies as a capture. We detect with a sheep polyclonal antiserum -- this is the same antiserum that is currently used for the RID -- revealed with an HRP conjugate.

And these are some data demonstrating that where we are with the ELISA, which is that we're comfortable and ready to move forward with it. So these are the three capture antibodies, which are labeled alpha-F51, 110, and 117 in green, purple, and blue respectfully. And in this case what we did was this was native Fel d 1 that was purchased from a vendor, and so the concentration increases -- and this is the OD_{450} on the Y-axis. And as you can see, these three antibodies all have a nice sigmoid plot in response to increasing allergen, but the alpha-F51 is clearly more sensitive. It's a much better capture antibody, a higher affinity capture antibody by about a log than the other two.

Now note that for our particular purposes this difference is probably not important. We're dealing with extracts. We know the concentration the range. We're not looking for sensitivity. What we're looking for is a nice linear range in which we can measure the allergen, and all three of these capture antibodies give us this.

Having done this with native Fel d 1, we went

ahead and did it some cat extract to make sure that it worked in that instance as well. The important point about this curve is that now we have dilution of the cat hair extract, so the concentration is decreasing as we move to the right on the X-axis. But as you can see, again we got our nice sigmoidal curves, and the alpha-F51 demonstrates enhanced affinity for the allergen compared to the other two.

As far as three antibodies that we chose for studying with Amb a 1, again, all three of them worked very nicely. They all worked within the range that we could easily use for measurement of the major allergen within ragweed extract. Some appear to be more sensitive than other, but whether or not that enhanced sensitivity has relevance or importance for our particular purposes, I'm not so certain.

So what are the next steps as far as moving forward with this? Well, we wanted to select which one of these scFv's to actually use. If we can determine that one of them is more relevant to the allergenic sites on these proteins, then that would be a determining factors. And under those circumstances,

we're planning to look on a Western blot with cat because we know that the allergenic activity is on the alpha chain, and we're going to conduct some basophil stimulation assays to determine whether or not any of these antibodies might block basophil stimulation better than any others.

If none of those really give us any solid results, then we simply choose upon which antibody grows best, which antibody we can get the most of for the least amount of work. After that, we prepare a validation program, a protocol. We perform the validation. We invite manufacturers to participate in the assay validation, summarize it, and then prepare at least 20 g of each scFv that we're going to use in aliquots for distribution throughout the next many years as we adopt this particular assay and move away from the RID.

And that's the end of this presentation. I'm happy to take any questions.

DR. HAMILTON: So I missed the detection antibody. Is that a polyclonal antibody?

DR. RABIN: Yes, that's a polyclonal sheep

that we're going to use that we've been using for the RID. We actually have given the much lower quantities that are necessary revealing here. I think we calculated that the lot of each that we have will last seven or eight years, something along those lines. So given that and the monoclonal nature of the capture, this is going to take a lot of pressure on the reference replacement program.

DR. HAMILTON: Well, first, I want to commend you on this move. I think it's absolutely timely and very appropriately, and certainly we'll move toward a more quantitative and more reproducible assay I think over time, so good. Any questions from the Committee? Dr. Grant.

DR. GRANT: I notice the focus on grasses, and I guess that's necessary. There certainly Timothy has been a standard internationally, and I would hate to see this focus on so many grasses prevent the laboratory from expanding the panel. We have patients with desperate allergies to many other things that eventually need to be standardized because we don't know that we're giving the right thing to patients.

So one thought would be to abandon red top, June, perennial, orchard, and go with one so that the focus of the laboratory then can expand and help us do rational diagnosis and immunotherapy to everything our patients are suffering from.

DR. HAMILTON: That's a very good point, Dr. Grant. Dr. Rabin, can you speak to the issue of expanding the repertoire and maybe targeting less grasses because they cross-react with each other and focusing on a broader spectrum of allergens?

DR. RABIN: Yes. Okay. I haven't given any consideration toward the cross-reactivity of grasses and whether or not we can discard any of the assays. So having said that, I'm not going to comment on it, but I will give it some thought. I think we can give it some thought and some discussion.

As far as expanding the number of standardized allergens, we are certainly interested in doing that, and we have discussed with the manufacturers at the yearly meetings that we have with them potential routes of doing that. I don't know that we have the resources to really do the investigations to set up doing

standardizing new allergens, and we've looked to the community for partnership on that, and where this is that we've discussed it.

But I'm interested in doing it. I think the first thing that one has to do is one has to look at the science and where the science specifically states that one or two proteins can be used that mediate the allergenic properties of the particular allergen because I think that that's really a better place to go with those particular allergens rather than to develop more competition ELISA with more biologic sera pools and such.

So that's where I'm hoping that we move with it, but CBER cannot do that kind of assay develop all by itself.

DR. HAMILTON: During our site visit, we had the pleasure of having a perspective on the resources that the laboratory has, and the resources are defined constrained and applied. You're suggesting maybe targeting fewer and expanding in a different way, but clearly additional resources would probably have to be given to the laboratory for them to expand their focus

in allergen specificities I suspect.

The question I have: Since food allergy is such a big issue and there is such variability in the food allergen extracts that we use, is there any thought to focus or turn your attention to the three major allergens, peanut, egg, and milk? Or is that a black box that is going to remain a black box for us for a while?

DR. RABIN: We haven't given any thought toward developing standardized allergens to that. Certainly, we are spending a lot more time thinking about food allergy in particular. That's for sure. I can't say that the food allergy community that this is something that they've raised, okay, in terms of coming to us and saying that this is something that they would want to do. So without a demand from the scientific community, certainly the idea hasn't occurred to us.

DR. HAMILTON: Dr. Slater.

DR. SLATER: First of all, on the issue of additional standardized allergens, we actually had a fairly full discussion of it in the Advisory Committee. It was probably 2002, and we went through a number of

different possibilities. Among them were some foods, some molds, cockroach; and at the time, there was really no push that I can recall from the Committee about introducing new grass pollens among the standardized allergens although I think that's an interesting proposal and one that can be considered.

One of the interesting things about this entire process is that appropriately I think it's science driven. The push toward standardizing cockroach really came at a time that the data were first becoming available the cockroach was a fairly important allergen and well-defined population that seemed to need some relief in terms of rational allergenen in the therapy, and that was intercity asthma patients.

With foods, we may actually be science driven to do some standardization over the next five or six years in the sense that there is a lot of work both scientific and clinical/scientific that is identifying really critically important allergens for some serious food allergies, so we may be in a fairly good situation with some of the foods as we were with cat and ragweed

where we had a pretty good idea what the important allergens were, and standardization could become a fairly straightforward matter.

But I think what Dr. Rabin is pointing out is that this is an iterative process. It's an interaction between what we perceive as the public health priorities and what the scientific community is generating in terms of interesting science that would hopefully coalesce around certain future standardization products. But these are all interesting ideas that I think we need to discuss at future meetings.

DR. RABIN: I would state though that any new standardized products would obviously have to be done in the context of the quality systems of which we spoke, and therefore we would undertake such a thing until we're completely accredited and done with the rather huge task of completing our quality system development in-house.

DR. HAMILTON: Dr. Grant.

DR. GRANT: You mentioned that your laboratory is responsible to the public input. Having practiced

allergy for nearly 40 years, I would bet that there are 50 or 75 million Americans who would love to have some science put into the area of food allergy. So I'm sure if you asked for that input you'll get it. This is a big area, and my ability to diagnose these people is where we were with ragweed, say, 50 years ago, so we're five decades behind, and I would love to see that this be considered again.

DR. RABIN: Well, thank you. I appreciate it, and your input is heard. We hear it, and I would state that we do communicate with the scientists and clinicians and the translational scientists who primarily focus food allergy a lot, and I suspect that we will have conversations with them in this regard in the future. So thank you very much.

DR. HAMILTON: Yes. Dr. Self.

DR. SELF: This is a very interesting discussion. Dr. Slater mentioned the magic word to me, which is public health, and it seems to me that that's the science that should appropriately drive prioritization of what allergens are here. And I'm not sure I've heard in this discussion a systematic

approach to assessing the state of public health science in this area and informally using that to prioritize the allergens within the constraints of the budget and all of that, so I would suggest that --

DR. RABIN: Well, thank you.

DR. SELF: -- if that's not being done, that be a done --

DR. RABIN: Okay.

DR. SELF: -- in a little more formal way.

DR. RABIN: Well, thank you. Certainly, the allergens that we showed you are, of course, the allergens to which -- except in trees -- to which most allergic people with regard to environmental allergens are allergic. So in that context, even though it's a very small percentage of the number of licensed allergen extracts, it makes up a large plurality, I'm sure, if not a majority of those that are actually distributed.

So I think sort of in an informal way that is being addressed, and in the ones that we consider, the ones that I've been considering and thinking about and the ones that we've discussed today such as food, that

certainly is the approach. As to whether or not there is no formal approach, and I would be interested in hearing -- perhaps during the break, you could share with me what one might be.

The other thing, of course, it has to be taken into consideration is whether or not it's doable. Unfortunately, with cockroach, as Dr. Slater work is finding it, it might not be, and so we have to choose the lower hanging fruit as well as that which we would prefer to eat.

DR. HAMILTON: Good point. With regard to the food, right now we have a tremendous amount of knowledge about the components in peanut, egg, and milk, and many of these are purified. So the major allergens are known, and I think supplying some of your new technologies with the bead-based technology, which we're going to I think hear about later, could very well be of great benefit for all of us.

One more question. Dr. Saper.

DR. SAPER: Thank you very much, Dr. Rabin. With respect to foods, I'd like to reiterate that that is something that is very much in the public interest

and the public mind. There are things that you know are quite different about that however, so I'm not sure that what has driven the standardized program for the aerial allergens is that we have had therapy for that, immunotherapy, and we're looking at how we're using this therapeutically.

In terms of foods, that will be a different structure going forward in terms of treatment and what you include and how you include it because, again, these are the things that you find in the grocery store, which is where patients are going to want to end up. They're not going to want to end up on the shots. They're going to end up on the food.

In terms of the biologic activity, when you're trying to do skin testing, we know that the skin testing for the air allergens has much better clinical predictability than does the food.

So there are a whole host of issues that make this be potentially a different process in that there are two things. With the ISO 17025 accreditation that you're going through -- and I applaud you. I think that's an excellent project -- and that something

that's iterative and continues over time and has periodic accreditation. And as you go through that, when we get to a point where foods can be put in this, then you're at a spot where you can make your protocols, test your designs, and put it through that ISO process, which will make it easier.

But I do think in terms of this being driven by what the population and the patients need I think that the fact that it's somewhat of a cottage industry within the area of foods that I think having the initial thought process within your regulatory purview is probably very important and very timely.

DR. RABIN: Thank you. I think that point has been made clear, and I think we will consider it, and we thank the Committee for that input. Thank you very much.

DR. HAMILTON: Great. With that, I'd like to suggest we take a break for a period of time. We'll reconvene at 10 o'clock -- oh, no, 9:45 since it's now 9:25.

(Off the record)

(On the record)

DR. HAMILTON: We'll reconvene our meeting. Now going to turn to a presentation on the statistical consideration of the design and interpretation of Phase III Clinical Trials by Dr. Tammy Massie. Dr. Massie.

DR. MASSIE: Am I on?

DR. HAMILTON: Could you just give us a brief overview of your background please.

DR. MASSIE: Oh, certainly.

DR. HAMILTON: Yes. Thanks.

DR. MASSIE: I am Tammy Massie. I'm a mathematical statistician in the Bacterial and Parasitic Allergenic Team. I have been with the agency just about nine years, and I've been a team leader for about a year and a half now, so hopefully that gives you a little bit of background about me.

And I want to thank you for the honor privilege of presenting today. Hopefully, this provides some illumination about the statistics as well as the statistical analysis of allergenic products.

My goal today is to talk about statistical concept, and what I'd like to do is I'd like to say that I'm going to talk about basic statistical concepts

or moderately basic statistical concepts, and then I'll apply it to the allergenic setting. I have a whole bunch of graphics to promote the different statistical concepts and kind of an illustration of a potential allergenic product, and all of these are just simulations. They have could reflect reality, but they're not based on any specific product. They're just a pure simulation just to give you a heads up.

So as you've read the goal, hopefully, you'll know that we're going to start with the statistical concept then go to the application.

When you're talking about statistics, you have a whole bunch of different data sets. The data sets that we're going to focus on today are the continuous data, the longitudinal data, the survival data. Those are the ones that are mostly likely going to occur in allergenic products. There are other ones including categorical data, but frequently, we turn categorical data into continuous because it's a scale of zero to 30 or zero to 100 or things along those lines. So there are one specific response, but we -- a statistical framework is pretend essentially as though it's

continuous, and that it's generally acceptable and needs a little bit of thought and discussion, but certainly it's -- so that is why I'm talking about those thing.

And I'll talk about the important measures, but the last three topics -- the bias, covariates, missing values, and hypothesis testing -- I am not actually going to present slides on, but hopefully you'll capture in my presentation the different thought processes and how those can be applied to allergenic products.

What you have here is you have your generic general curve. This could represent data, and so what you can do is you can kind of look at this data, and you can see that this is a very small variance relative to the other ones that I've presented here for continuous data. In other words, you can have this scale and are pretty centralized about this one particular point.

In the next situation, you see sort of a medium variance. In other words, that data is a little more spread out. And finally in this sort of red, this

is a larger variance. And ideally, as a statistician, I like the smaller variance.

Now what this could do, if you can talk about this larger variance, and so you can look at data, and this could be response to something along the lines of maybe people's response to poison ivy, and so you would run through a poison ivy field -- a whole bunch of people do -- and you can have people who just don't get poison ivy because they're so lucky. You get the people who kind of get response like right around their ankles, and then you get the people who are just covered with itchiness all over.

This would have a very large variance because you have all different people in different types of response, but then you could talk about maybe that just central group of people, a subset, where they're a little bit responsive; they get the poison ivy around their ankles. And if you just looked at those patients or those individuals, you'd have a fairly small variance; where if you looked at every single person, you'd actually have a moderately large variance. So that's something to consider.

Now in addition to that --

(Pause)

DR. MASSIE: Oh, I'm sorry. Thank you. I'm not sure I'm capable of doing two things at once. Hopefully, I can.

So what you have here is this is going to just be a comparison of two different groups. And what you can see in this first grouping you can see that this is going to have two different means. They've pretty well split apart. Like I think if you had two treatments groups and we all saw this, and we could see that this was a meaningful difference, you'd say, "Oh, yeah, there is definitely a difference. On the other hand, where you see this second graphic, what you see is slightly different means, but it's not that spread apart.

And finally, in this last situation, you can talk about something where it's a fairly large variance in that first group; and in the second group, it has a smaller variance. So as an illustration or just to think about, this could be something along the lines of placebo. And placebo effect, that ends up being

sometimes fairly substantial, and then you can have a fairly effective product. So in other words, you can see that this is fairly narrowly defined its response; but because of the fact that there is this fairly substantially placebo effect, you're not going to be able to necessarily tease out that difference.

So one of the things when you're starting to think about running studies and you're trying to get into the Phase II arena, if you want to run some pilot studies, if you want to run some Phase II studies where you make that if you're seeing something like this you get this adequately powered; you get an adequate sample size so that you actually can start detecting real differences.

I'm sorry. I apologize for not scrolling forward. I'm now kind of dyslexic.

So like I said, there can be inadequate sample size or lack of power or improper subject selection. You can end up with people who are not responsive because maybe you haven't look at the proper target group. And like I said, pilot studies or Phase II studies can certainly give you some background which

group you should be looking at so that you can ideally find this situation.

Continuing on, I promised to do a little bit of continuous data. In this particular case, what I'd like to do is I'd like to just kind of give you a verbal example. This could be something along the lines of the explanatory variable is pollen count, and so you can think about, "Okay, pollen count goes up and up and up over the course of days." I think that here in D.C. we're just way up here. It's just miserable. Everything is covered in yellow, and the response variable could be something along the lines of you symptom.

So what you can see is as your pollen count goes up clearly the symptoms go up. There are some people who have less symptoms. And you might say, "Oh, that's a nice graphic and that's all pretty," but what if I told you a fact? What if I told you that these are two different groups? And in fact what if you saw I've colored them slightly different, and I've also tried to create two different things, the diamonds and the triangles.

And so what you can see is that here you have two different groups. Now if beforehand you didn't know this but I did -- because I'm a statistician and I know this information -- what if these were two different genders? Like what if you had more responsiveness in males, perhaps, than females? This can lead to bias because you don't necessarily know that that occurred.

So what if in the worse-case scenario, you ended you randomizing a whole bunch of females, but they're not responders really; like they have less aggressive response. And alternatively -- so that explains bias.

On the other hand, what if this was two different treatment groups? If this was two different treatment groups, I think we could all kind of say, "Yeah, there is separation between these two different things." So it depends on the situation. And like I said just a few moments ago, a good, well-run pilot study or Phase II study can tell you if there is something underlying that can influence it. Because remember, if these are two different groups, and you

didn't know that this difference existed, then your variability will be big. Ideally, you want that small variability, so that could create some issues.

This one I won't focus on very long at all because it actually pops up a little later in slides, but this is just longitudinal data, and this is just data that's collected over various time points.

Another type of data that you can consider when you're talking about allergenic is survival data, and it can be time until death. So in the food I think that you can end up with allergenic, or you can have allergies such that you eat something, and it really becomes catastrophic.

On the other hand, in the pollens, in the ragweed, and the molds and things like that, you can talk about time until you have hospitalization. You can have time until you need rescue medication. You can alternatively have time until what symptoms are are just pretty much unmanageable, so you have to take a day off from work or day off from school or things along those line.

So those are considerations. Those are data

that you could collect when you're talking about these allergenic products.

And as I've discussed these, going through these fairly quickly, like I said, there are different biases. There is confounding and covariates. Covariates are just variables, so that can be gender; it can be your preexisting conditions. It could be how allergic you are if there is some kind of scale or mechanism. So these are these are things that you can consider. You can also consider centers because certainly bigger centers and smaller centers sometimes do have an effect on your patients.

And then missing values. I didn't really highlight those, but they need to be considered, and I actually will highlight those in the allergenic example that I use. But some solutions are really a well-designed prespecified study. If you've done pilots studies, if you've done Phase II studies, you can hopefully find out the optimal treatment time. You can hopefully find out how often you need to give the medication as well as how often to investigate what the symptoms are such as if you want to do it once a day,

once a week, once a month. If you talk about doing things too frequently, you'll end up with missing values; of if it's too overbearing, you'll also end up with dropouts, which essentially are missing values. And you have to kind of play a fine line between those to make sure that your study is going to really work to the full effect of the study, and you won't have these issues. And like I said, you'll need clinically meaningful end point; and you'll need, as I said, an appropriate timeframe not necessarily too long or too short. You want to be like Goldilocks: You want it to be just right.

So here we continue on with the statistical concept applied to allergenic products. In this one, I'm just pretty much talking about more of the pollen just because that is where my familiarity is. And you can talk about the safety end points, so just the adverse event. And then you can also talk about the symptoms. Frequently when we talk about the symptoms, we combine the symptoms for as well as the use of rescue medication into one combined symptom and rescue medication score or comprehensive one.

And so when you think about that, what you can do is you can collect that data over time, longitudinally analysis, as I alluded to earlier, and you can see that in this particular graphic what I've done is I've actually looked at two different groups -- I simulated this -- and you're starting from sort of initiation of allergy season, and you can see over time these two different groups separate somewhat. In this particular case, I gave a fairly, hopefully, effective treatment because I was simulating the data, and placebo. You can compare those results over time. Here I just used week, but depending on which allergen it is, it could be days, it could be weeks. If it's an exposure that fairly consistently occurs, it could be longer such as months.

So here what I've done is actually I've superimposed the simulation of my allergenic season starting with this baseline time period and then how the allergy has kind of crawled up over time; the pollen count has crawled up over time. And you can see here, again, you see that separation between the two groups because when you're simulating data you can make

it do whatever you want.

And here what I did was I actually looked at some of the responses of the individuals. Notice here that there is some variability, but actually if you kind of look over here -- because like I said I was creating my own simulations -- I tried to actually make it flat and out toward the end of this time period. Where on the other hand, this other group it's sort of it's still there having a modest amount of variability.

When you consider this data, you can also look at the confidence interval, and the confidence interval is fairly useful because it tells you where the mean is, so that middle dash is where the mean is actually. And it tells you how spread out the two difference data points are. And I think that here -- continuing on -- what you can see is that the mean of the two different groups here is fairly substantial at this end point, and at the very beginning, it's actually is in the opposite direction, and here you have a little bit of separation between the two groups. So you want to kind of keep this little vignette in the back of your mind as we continue on. But here what I can do is I

actually can plot the end of the 95-percent confidence interval, and you can see that here there is a dramatic amount of overlap between the red group and the blue group. Once you get down over here, you see that the red group and the blue group have a fair amount of separation.

And what I'd like to tell you right here is that these are the confidence interval of each of the different groups. And the 95-percent confidence interval means there is a 95-percent probability that the confidence interval contains the true value of the population parameter. So basically what I'm trying to tell you here is that the data right here, the mean actually could potentially be down here, and the mean of this group could potentially be there. In other words, you could have this very tiny difference between those two if everything is going horribly awry in your statistical world or your reality or whatever. So it's something to be kind of cautious about. You can detect for differences. You can test for differences, but you can actually have a detected difference, but it can just be very, very narrow.

So continuing on, if you talk about the 95-percent confidence intervals of the differences, you can see that suddenly instead of that fairly large gap that we were looking at before it actually goes in the wrong way. That first one is so tiny, and that second one here it's starting to get up there; in this final group, you can actually -- I think there is plenty of light space. I think I could go home fairly happy if I saw something along those lines if that was the difference that I hoping for.

So the examples, both those verbal examples early on when I was talking just the generic statistics, as well as this example of pollen count over the season with these two different groups, there can be difference between the degrees of separation. And when examining means and standard deviations, just looking at the means and the standard deviation may not be sufficient because you need to account for the variability. It can be that the variability, like I said early on, you really want that variability to be fairly small, but that may not be assured in a real-world study, in the real-world situation.

So continuing on. When I talked about those differences, that little white space between the two different groups, that's the differences between the two different groups. There are several scenarios that can occur, and what I'd like to do before I talk about those scenarios -- this just comes straight from the previous graphic essentially -- is that there are different things that you could be interested in looking at.

You can be interested in looking at the noninferiority margin. What the noninferiority margin is and when you consider it is when you're looking at two different treatments, when one of the treatments is an approved comparator, it's already on the market, you already know it works because it's approved, and the new product is comparing to this approved comparator. So you want to be pretty close to what that approved comparator is, and you can be just a little worse. So in other words, if you're talking about cars, you can compare perhaps a Civic to a Corolla. The Corolla you know gets about 35 miles per gallon. The Civic get about 35 miles per gallon, but if it 34 miles per

gallons, you can live with it even with gas prices at $5 a gallon. So that explains noninferiority margin.

The next value that's of interest is going to be zero, or that is what we would call statistical significant difference, just pure difference, not difference by a specific amount. In other words, you can see a difference between the two groups.

And this final hash mark talks about clinically meaningful margin, and a clinically meaningful margin is going to be the sum margin when you are comparing a treatment to a placebo. So this is when you're comparing to placebo, and you want it to better than a certain amount. You don't want it just to be that you have an allergenic product that reduces your symptoms by near minutes; you want it to be clinically meaningful whether that's a few hours, whether it's a few day, or whether it on a scale is quite a few points. So in other words, this clinically meaningful difference is not just zero; it's a bound that you really want to ensure that this product truly is effective, that it shows what is desirable and useful.

So continuing on. Whether you use a noninferiority margin, just statistical significant, or a clinically meaningful margin, it's going to be determined by the type of study you're running, the comparator, the anticipated safety. If you have a product that really has a lot of perceived risk, you probably want a fairly substantial clinically meaningful margin and the perceived efficacy and the benefit/risk profile. So all of these things are some things to be considered.

When you talk about a clinically meaningful margin as a sponsor -- so anybody who's proposing any new products -- it would be proposed to the agency, and then the agency would discuss it, and ultimately that clinically meaningful margin would be determined and agreed upon.

So here I reiterate from before we had the little situation where there really wasn't the two differences between the two treatment groups at time zero. And so here, you really don't see any difference between the treatment groups. It actually doesn't even meet that noninferiority margin, but that was not

expected because of the fact that these were two treatment groups at baseline, so ideally you don't want to see a difference already occurring.

The second situation was that situation where it was about week 4 or so, and that did actually meet an noninferiority margin. So in other words, if you were comparing two groups where one of them was an approved comparator, yes, it's noninferior to the second group.

The next situation actually did have difference. You could see that little bit of white space between the two groups. And here you have statistically significant difference, but it might have been marginal; you might have gotten a few extra moments without needing a tissue or something along those lines. It wasn't clinically relevant or clinically meaningful.

And then that final situation where I think it was about week 12 or so, you could see that there definitely was a difference between those two different groups, and really it very relevant, and it was fairly robust and fairly large.

So a summary of allergenic examples. Pretty much the lower bound of the 95-percent confidence interval greater than a prespecified threshold ensures reproducible statistical significance that translates into clinically meaningful difference. In other words, you've got this value that's preset, prespecified; and if you meet that, then you are showing what you've desired to show as in a Phase III study.

And for illustrative purposes, I basically showed you where you could see the two different groups splitting apart, but you do need to select a timeframe that you could have missing values. You need to account for that because in missing values we really wouldn't know does it continue to split apart. The missing values are they really going back down to what the origin was? Is it people who are missing is it because their symptoms have come back full throttle? Or is it because they're miraculous so cured they don't need to come back.

So you really need to consider what timeframe will you minimize those missing values whether it's missing values for good things or for bad things

because we don't know. As a statistician, missing values are the ban of my existence because I don't know that they mean. I don't know if there are great reasons or for bad things.

The consideration of standards. When we are looking at difference between two different groups, we can talk about the lower bound of a confidence interval, which is what I presented here. I think hopefully I've presented a rationale for why you want confidence intervals. I think that that provides information, and it provides not just the mean, not just the standard deviation, but how far are these two different things separated.

Alternatively, you could do a predefined difference between groups based on a specific value or a specific percent change; but there, you could end up saying you need these values to be very substantial, where perhaps in the lower confidence bound you can have a smaller value. So in other words, there is a tradeoff between a specific difference or the lower confidence bound.

So in that first picture where I had the two

normal curves, I think that when I set up those two normal curves, I had a difference of a 3-point scale. But what if the desire was to see a 10-point scale, then even seeing those two separate, normal curves wouldn't have been beneficial anyway; like clearly they were separate, but they weren't separate by an adequate difference in adequate value for that.

So we can consider p-values. P-values are the probability of observing a result as extreme or more extreme than one observed giving the null hypothesis is true, but it might not be adequate. On the other hand, confidence intervals given estimated range of value in which it is likely to include the unknown population parameters, the estimate range being calculated for a given set of data samples. It essentially provides a range of the magnitude of effect and an estimate of its reliability. It provides an awful lot of information when you look at confidence intervals.

So in conclusion, hopefully in the presentation I've given you some basic statistical concepts that might be applied to allergenic products. Hopefully, I made it so that you can think about if you

decide to set up studies, particularly more advanced studies, Phase II or Phase III studies, that you need to do your homework, you need to do you pilot studies, and you need to think about all of these things all simultaneously. You need to account for covariates. You need to have a meaningful difference. You need to consider what the appropriate timeframe is, when you actually start seeing the allergenic product kick in, so that you can see that separation.

If we had looked at that allergenic product that I had simulated, in those first two or three weeks, you're not seeing a separation because really the allergenic season hadn't occurred. So it's critical that the meaningful difference as a target in the protocol is critical and should be agreed upon before the study is implemented.

All of these different covariates -- the bias, the missing values -- should also be considered when creating that protocol. And ideally, it all works out, and the reality is similar to the presentation that I gave here.

Thank you very much for your kindness for

inviting me here. I'd also like to thank my management chain and the opportunity to present and, of course, my husband, who also is a statistician who has been ignored for the last week or so.

(Laughter)

DR. MASSIE: Thank you.

(Applause)

DR. HAMILTON: Thank you, Dr. Massie. Will you remain after Dr. Rabin's talk so we can field questions for both of you together?

DR. MASSIE: Certainly.

DR. HAMILTON: I would appreciate it. Thank you very much. Dr. Rabin now is going to give us any overview of the environment exposure chamber issue with regard to Phase III studies for allergenic products. This has been in the works for a while. A lot of thoughts have been given to it, and I'm looking forward to this presentation very much.

DR. RABIN: When we consider what is necessary to demonstrate a new product for allergen immunotherapy for seasonal allergens, the study must be a well-designed, double-blind, placebo controlled study.

Generally, there's a comparison of a placebo to not only a placebo but to a baseline year. We do accept combined symptoms and medication scores as the primary end point, and the studies must be adequately powered to take into consideration expected differences between treatment and placebo, which are generally not great, and the expected variability of each group, which is fairly high.

So there are impediments then to demonstrating this level of efficacy. One is the subjective nature of symptoms scores or combined symptoms and medication score even, accepted differences between the placebo and the treatment groups, and that requires that these pivotal trials have to be fairly large and requiring multiple study sites.

To induce the symptoms of environmental allergens, seasonal environment allergens, the pollen levels at each site has to be high really and if you have a baseline year then for two consecutive years. Our concern has been that given all these factors there may be truly effective agents in which studies will fail to demonstrate efficacy because of one or two poor

pollen seasons.

These are some data that were recently published by the group at Walter Reed here in Washington, D.C., and what they did was they looked at a 10-year profile of grass and weed pollens in this area over 10 years. According to the scale, you can see that they've sort of color coded the peak with red and increasing levels with green and yellow and blue; and you could see that the grass season, of course, has we do know, is fairly wide and is about to peak within a few weeks. For example, the ragweed season is a bit narrower and peaks really very much closer to its onset.

Just to fill out the information, trees really vary quite a bit according to species, with tree season for the most part peaking from late winter into early spring but with some variability according to some of the species, elm in particularly being kind of interesting because it has this biphasic pattern.

Grass can actually be a little bit biphasic as well, having the small peak in September, but what's most important that I'd like to point out to you about

this graph is that these are then the pollen counts as they vary from year to year; each year is color coded. On the X-axis, we have the month; and on the Y-axis, the actual counts. And what you'll notice here is that there is a lot of variability within this one geographical area, the Washington, D.C., area, as far grass pollens are concerned.

So there's one year in which the peak was 8; there are a number years in which the peak was around 20 or between 20 and 30, the peaks tend to shifts. That's true for oak, on the top, and even one that we generally think of as a real hard and fast, consistent standby rock, ragweed, can vary very much; it can shift a little bit; the peak can be wide in this case or fairly narrow as we expect it to be, so there's a lot of variation from year to year in these pollens.

And so these pollen counts then are highly variable within this region, within this single region. Imagine a study in which you have a number of study sites across multiple regions such that the variability in the seasons increase, the variability of clinical symptoms enhancing the possibility, again, of a failure

to detect efficacy in a therapeutic that truly has advocacy.

So that brought up here in the LIB to consider the issue of environmental exposure units or chamber as they've sometimes referred. And in general, these are contained rooms in which the exposure to airborne substances is controlled, and there are some advantages to them. Studies aren't limited to the period of natural pollination. They can allow, theoretically at least, for control and uniform allergen exposure. There's no impact of weather conditions; no impact of personal context, whether or not people spend their days on their bicycle or at their video console; ensured compliance; and timed symptom assessments.

There are a number of environmental exposure units throughout the world, and this is just a smattering, an example of some from a recent review, and the point here is that they come in all different sizes, from the very small one in Copenhagen that can contain one subject to one in Atlanta and the one in Kingston, which takes about 150 to 160 subjects. There are some differences in the ventilation systems. There

are differences in the amount of the allergen load, and there are differences in the methods in which the allergens are monitored.

The picture is worth a thousand words. This is a picture of one of those units. This is simply an example of in this case the one in Kingston, Ontario. So what you have here is this schematic in which you have these fans that blow air out and circulators and the seating area here and so on, and you can see these clearly very comfortable chairs that people would sit in for a period of time while they're being monitored.

When we consider the possibility of using environmental exposure units for clinical trials, a group of allergists met in 2009 to explore this, and there was a consensus that the EEU's may provide uniformed distribution of pollen; but that larger units would require more monitoring; that you may be able to use some objective criteria within these units because the subjects are all collected in one place with study personnel such as peak nasal inspiratory flow for example; a priming phase would have to be included if you're studying seasonal allergens; monoallergic

subjects would be unnecessary, in this particular context they wouldn't confound the study whereas with grass and ragweed that can be an issue; but that natural exposure studies may also be necessary.

In February the following year, last year, the NIAID met with stakeholders to consider further this issue. And the consensus there was that standards need to be set and harmonized, standards for these units; and right now they're not; and this would require a amongst those stakeholders sharing of data, obviously without sharing intellectual property.

And then last June, NIAID hosted a workshop with the stakeholders in which the attendees agreed to prepare a published document to discuss further the need for EEU validation and to consider preparing collaborative grant applications to fund these studies, the first of which would be a comparison of the effectiveness of common seasonal allergic rhinitis medications in the EEU versus natural seasonal allergen exposure. And then the second would be determining the inter-EEU variability under standardized allergen exposure conditions.

This chart illustrates our approach in general toward allergenics and whether or not the exposure to allergenics would be controlled or natural as we consider them for licensure. For food and for venoms, we really would very much consider controlled exposure to the allergens as that's what's most appropriate to determine whether or not there is an actual symptom response. For pets and mold, which are not seasonal allergens but perennial allergens, we certainly accept natural exposure data, but we're open to discussing and considering exposure in controlled environments as these are perennial allergens and as their levels can vary with location even within a geographical area much more than a seasonal allergens.

And with pollens, of course, we now certainly accept the natural exposure data, and we are, as I've outlined to you, in our current stage of thinking about what the issues might be regarding controlled exposure in these units.

So in summary, the units are potentially an attractive tool for proving efficacy of novel products for allergen immunotherapy. The studies in the unit

may not be sufficient alone for demonstrating efficacy. Natural exposure studies may continue to be required. But there are some outstanding issues. Validation of even distribution of pollen throughout an EEU, harmonization of standards amongst the different facilities in North America and Europe, and also consideration of what the contribution of behavioral aspects of a group are toward the bias of data.

We've done a lot of thinking with regard to this, and it's certainly hasn't been me alone, and I want to thank Jay Slater and Paul Richman from within the FDA for contributing toward our evolution of thought regarding this issue. And also really it's been a very good collaboration with Alkis Togias, Marshall Plaut, and Matthew Fenton in NIAID. Thank you.

DR. HAMILTON: Thank you, Dr. Rabin. These two presentations are now open for our panel discussion. Dr. Self, can we start with you to give us a feeling for your perspective on the issue of confidence intervals?

DR. SELF: Well, there's not a whole lot to

say. I think the use confidence intervals to supplement p-values is pretty standard practice, so I think there's not a lot of discussion that required there.

What I find most interesting is the applications to these trials, so if you don't mind --

DR. HAMILTON: Please.

DR. SELF: -- I'd go ahead and start --

DR. HAMILTON: Absolutely.

DR. SELF: -- asking some of those questions. The statement of the problem is in two parts. One is the expected differences for environmental exposure efficacy trial; the expected differences are small. And so I guess I'd like to hear a little bit more about that because it's a little surprising that you're going after small differences. So that's one.

And then after I hear that, I'd like to asks a bit about the next point, about the expected variability being high. So you want to start with...

DR. RABIN: Okay. Well, generally speaking, about a 25-percent improvement in symptoms and medication scores all statistical issues having been

addressed is acceptable, and that's not a huge change necessarily when we consider other licensed medications. And I think that in part acceptable because the variability is large.

If you think about it, if you take symptom score alone, you can imagine -- I'm sure you could think of amongst your own acquaintances two individuals who experience the very same level of symptoms but one of whom would consider it impairing in his or her life, and the other who would just blow it off and bring a box of Kleenex. And it's not to trivialize one or the other, it's just to simply say that people do rate these things differently, and that the threshold for taking a medication is different. Okay. Some people just don't like to take medications, others do.

The idea of combining them is hopefully to minimize that variability, and I suppose that it does. I'm sure that it does, but it's not ideal. Until we have good, objective surrogate data -- and there are studies out there, and one of them coming from Dr. Durham's lab, that's something that we can really measure. As long as these are based on subjective

sorts of criteria of how people feel and whether or no they take medications, you're going to have a lot of variability.

DR. SELF: So when you see differences are they -- it sounds like you're --

DR. RABIN: Can I just -- before you go on, since I don't perform these studies, and we do have people on the panel here who do such as Dr. Cox, perhaps she could address this a little bit, the actual, the experience better than I can.

DR. COX: Well, my thoughts are that there are two different things here. There's the natural exposure studies where you have large populations having variable exposure, and variabilities in their threshold for scoring something high and taking rescue medication.

But I would think the environmental challenge chamber is a little different, and I don't think we have as much experience with it in terms of allergic disease. As you can see, there aren't that many. And I would suspect that we would see less variability because we're exposing all these individuals to super

physiologic levels, and we might see less variability under those circumstances. But I don't think we have enough studies that could tell us that because there haven't been that many done with allergen.

DR. RABIN: But that's the goal.

DR. SELF: See, here's what I'm going. I'm new to this, so the problems are stated with a small clinically significant difference and large variability to motivate this, so I'm just trying to understand --

DR. RABIN: Sure.

DR. SELF: -- a little bit more what the problem is that we're trying to solve --

DR. RABIN: Sure.

DR. SELF: -- before we get there.

DR. RABIN: Uh-huh.

DR. SELF: So just one more question about the difference. When you see differences in these studies, you're summarizing these by percent improvements, basically a mean, do you see more effects at the upper end of the scale, people who have much more severe --

DR. RABIN: Yes.

DR. SELF: -- that tends to come down --

DR. RABIN: Yes --

DR. SELF: -- and --

DR. RABIN: -- yes, yes. You do. And so a lot of times what ends up happening is that you have subset analyses where individuals -- and of course, again, we have people here on the panel in the back in fact who have done a lot of these studies who will either select for subjects who are monoallergic, okay, who are tough to get; but if you could find somebody who is monoallergic, then you have less of a confounding factor of other allergens and those who are more severely allergic, right. And then other times where you have a large study, okay, and then there will be some subset analysis where you can say, “Oh, let’s look at just the regions that have a pollen count above X.” “Ahh, here we really see the effect.” Okay. But unfortunately, at least currently, if the study isn’t powered for that sort of subset analysis, if that sort of subset analysis isn’t introduced in the statistical analytic plan from the outset, then that ends up being a problem.

DR. SELF: Okay. So let me separate two

issues. You went into kind of stratification, which --

DR. RABIN: Yes.

DR. SELF: -- I think addresses the variability issues, so there are things that one can do in designing these trials. I assume that is being done? That these are well-stratified, so that mechanism is being used to control variability?

Where I was going is that if the clinically important effects most of them are seen at the upper end of the distribution, summarizing by looking at the mean is maybe not the most sensitive or the most important measure. I'm just trying to probe a bit --

DR. RABIN: Okay.

DR. SELF: -- the extent to which some of these defects in the natural exposure studies might be remedied by a little better study design or definition of end point or primary statistical analysis, so --

DR. RABIN: Okay.

DR. SELF: -- that's part of where I was --

DR. RABIN: Okay. Dr. Slater --

DR. SELF: -- try to understand that.

DR. RABIN: -- had a comment, and I had a

question.

DR. SLATER: So the ability to recruit study subjects for these trials is sometimes a challenge, so whereas when these trials begin I would suspect that most investigators would look for the most severely allergic individuals that they could. That is typically without having a sort of wash-in period or a study season before you initiate treatment that's sometimes hard to guess in advance from either history or skin testing or blood test, and that will often exclude large numbers of potential recruits. It would be ideal obviously -- and I'm sure that all sponsors would love to be able to recruit sufficient numbers that they could stratify them in advance based on how they performed during the study; in other words, how severely ill they are at the outset of the study. But that's sometimes a major challenge.

And certainly having this discussion, this is a discussion that's happened before with these kinds of studies, and it's something that I suspect has happened before in this Advisory Committee in the past, but it continues to be, I think, a major challenge for these

investigators.

So getting around it in terms of optimizing the natural exposure design is obviously the best answer possible, but it may not be possible and is one of the reasons that Dr. Rabin is sort of introducing discussion of these more controlled exposures.

DR. SELF: Okay. Again, that's not quite to my point. I think there is an end point and --

DR. SLATER: Uh-huh.

DR. SELF: -- that there are some statistical things that it sounds like could be done that would improve this; may not probably enough to obviate the need for the controlled exposure studies, so let's go there, but let's be sure that we get all of the efficiencies that we can out of the natural exposure studies before we go there because I think it sounds to me like there are some more things that could done.

DR. RABIN: So I guess I'm just -- my curiosity is getting the best of me here, but what statistical -- you said, for example, mean might not be -- are you thinking something --

DR. SELF: Yes.

DR. RABIN: -- along the line of 75th percent? Is it something that simple or straightforward or?

DR. SELF: Something heading in that direction, maybe not something like that, but if you see in the control a spread and in the treatment group the lower end of that hasn't changed so much, but the most severe cases are being improved, that's an important signal that's not necessarily going to be seen by looking at the mean or 25 percent improvement type of metric --

DR. RABIN: Okay.

DR. SELF: -- so that's all I'm suggesting. I don't want to spend a lot of time because --

DR. RABIN: No, no, I understand. I was --

DR. SELF: -- this is not --

DR. RABIN: -- just curious where you're --

DR. SELF: -- the point of the session --

DR. RABIN: Yes.

DR. SELF: -- but I did want to understand the motivation and see if there were some things that could be done --

DR. RABIN: Okay.

DR. SELF: -- before we get into the control. Yes.

DR. COX: One of the problems with the natural exposure studies that we have seen is there have been years where there has been virtually no natural exposure, so you've invested the time, cost, setup a good study, recruited the patients, and there is no significant pollen exposures. And we've seen at three or four products run into that where there wasn't significant difference in the two groups in terms of symptoms.

DR. SELF: Yes. So there you can't do anything about that clearly --

(Laughter)

DR. SELF: -- controlled exposure. But again, there are a number of other reasons that were put forward. That one seems to be the key one though to me. So I guess my next question then has to do with the slide where you talk about the advantages of the environmental exposure units, and no disadvantages are listed, so I'm wondering if you could offer some disadvantages?

DR. RABIN: Yes. I think the lack of harmonization is a large one that's for sure. And the question of whether or not it applies to individuals, whether or not it applies to reality would be another. I would say that those are two large ones. The third one that I have some questions about, and I know there is some literature out there, but it's curious to me about the behavioral aspects of a group when you have that. I would almost -- if I had an unlimited amount of subjects, time, and money I would love to do a study where you could introduce a couple of serious sneezers into a group of 100 and see what happens to the overall scores and things like that because these are things that can -- we know that group dynamics affect how people feel, and we'd be interested in that.

But I think really that the units themselves at least as far as what we know there's some variability there, and we're not certain that you can apply knowledge from one unit to another. And if you can't do that, then that decreases the certainty that you could apply it to the natural situation. Jay.

DR. SLATER: There's one more disadvantage

that I can imagine, and I think it could almost always be surmounted by being aware of it, and that is that these are artificial units, and they are artificial units in which we are making an attempt to project on the natural world. Certainly, if there is a dose response and there is a -- we would imagine that the therapy would have a really pronounced, impressive effect at a very high dose, it would be our temptation to deliver that high dose.

If that high dose of allergen actually isn't encountered in the real world by the vast majority of your patients, there would be an overstatement of what the actual clinical benefit of the treatment would be. So being aware of that, being aware that this is an artificial environment but one in which we're trying to reproduce not the variability and unpredictability of the natural environment; but at least somewhere in that dose response curve, I think we have to be aware of that because it certainly would be an option to make a treatment look better by doing things that the patients certainly wouldn't encounter, and we do have a strong interest in projecting onto what the real world would

be.

DR. SELF: Of course, you don't have to just be aware of it; you can use that to inform the design, so you can look across multiple doses. You can make sure that those doses do calibrate to natural --

DR. RABIN: Yes.

DR. SELF: -- exposure across the different years --

DR. RABIN: Yes.

DR. SELF: -- and so on. So is that, those sorts of design elements all --

DR. RABIN: We've --

DR. SELF: -- part --

DR. RABIN: -- we've considered them --

DR. SELF: -- of the play here?

DR. RABIN: Well, I think that's really the purpose of this discussion. We've considered them in terms of proof of concept of considering the -- we've certainly had an interest -- let's put it that way -- in terms of graded challenge of pollen that would answer that sort of thing, particularly since we're dealing with therapeutics here that have a long-term

effect. We're not worried about the peak hay of antihistamine such that the serum concentrations fall after two hours or that kind of thing.

So graded challenges within an environmental chamber would be a very interesting way to do that. Remember, we don't design these studies. We approve them and we interpret them, but that is something that we had an interest in.

DR. SELF: Well, I think you're understating the impact that you could have on the design of these studies.

(Laughter)

DR. SELF: So --

DR. RABIN: Well, no -- yes, I have.

(Laughter)

DR. HAMILTON: Dr. Weber, any question?

DR. WEBER: Yes. I think there are several issues that come into play with comparing the natural exposure and an environmental exposure, and one is just the timing of the exposure itself, where in the natural exposure there is a gradual build-up. The season doesn't come on and peak quickly. For most pollens,

there's a gradual build-up, and so that there is in effect for the patients a priming period, and this has been pointed out in the environmental chamber things that you give patients an exposure in a chamber they may not have any symptoms without a previous priming. The problem then becomes what is appropriate priming. How much do you expose them to?

And that brings up the other issue that different pollens have different thresholds. For example, old literature suggests that most grass-allergic patients in a study will have symptoms when the grass pollen is over 50 grains/cubic meter. For ragweed, that's been suggested that that level is 30. If you look at data for olive pollen, it's somewhere between 150 and 400. So there are marked differences between what the exposure is in the natural setting and what degree of patients will then have symptoms at those levels. That probably adds a big impact on what the priming ought to be.

So these are not insurmountable problems, but it does point out that there're major differences between the environmental exposure, which tends to be,

again, a shorter time exposure, and then what the natural is where you have a presumed built-in priming effect already before you hit that period of where the sponsors says, “Okay, this is the season. This is when we’re going to measure those responses.”

The other thing that I thought was interesting was the concept of the mass hysteria within an environmental chamber where you have 50 people sitting there, and you look over and you see that guy three down is starting to rub his nose, you say, “Oh, is my nose starting to get itchy?” Yes. So you have whereas those people are just doing their scores by themselves at home, you could say perhaps that not as big an effect.

So there are all sorts of issues here, but I think they can all be weeded out. It’s just that these are not exactly the same situations.

DR. SELF: So is the goal to have a more efficient way of coming to the same conclusion that you would if you did an environmental exposure study of a sufficient size and during a high-pollen season or a normal pollen season? If that’s the case, then this

strikes me as kind of a classic surrogate end point type of problem, and the issue is to what extent can results from a controlled environment study of whatever design predict what one would see clinically in a certain year in a natural exposure. If that is where you're going, if that's sort of the gold standard for how you would use these studies, then it gets back to one of the early concerns, and that is that the difference that's determined to be clinically significant is fairly small.

And so whatever, however well you predict, if you're trying to predict a fairly small effect, that's going to be really challenging.

DR. RABIN: Right. So we can't -- it's the therapeutics that address the difference obviously, and the study we're hoping to affect the variability. But I think with regard to your question, I guess in thinking about it as you phrased it, yes, the goal is either as a surrogate or as an adjunct to perhaps to add to the data of a natural exposure study and enhance it and strengthen it.

They're also very useful in earlier phases to

rule out therapeutics. I think we've discussed here the question of, as I posed it, where you have a product that has efficacy, and it succeeds in a chamber; whereas maybe its success in natural exposure setting in marginal, and then the two together provide a package to the agency that, yes, this has efficacy. I would state that there is an instance that I didn't cover in here but is more intuitive, which is that if you have -- it's possible -- I'm not going to say categorically on the record -- but you could imagine that if a therapeutic doesn't work with a chamber that pursuits of a natural exposure study might be a little bit tougher to justify.

DR. SELF: So in sort of Phase II. It also strikes me that it might be conceptually easier to use the controlled exposure experiments in noninferiority types of studies rather than superiority, so you might also be thinking --

DR. RABIN: Yes.

DR. SELF: -- about targeted use in that --

DR. RABIN: Yes.

DR. SELF: -- area being a little easier to

do.

DR. RABIN: Yes.

DR. HAMILTON: Good. Those are really excellent questions and comments from the Committee. Before we open up the session to the open hearing, I'd like to ask Dr. Massie if she has any final comments or thoughts.

DR. MASSIE: I think that with the longitudinal analysis of the natural settings become, like you were saying, not only just using the mean or using some other variables, but then also thinking about it as a longitudinal analysis not necessarily just two comparisons of the end point or the peak verse the baseline, but considering that over a timeframe is something to consider.

But I think that in doing my statistics, I really glossed over the complexities of these studies to a certain extent and all of the different things that can infringe on them. Like I alluded to centers, how long the pollen season is depending on where you are in America. It's a lot longer in Southern states perhaps than in Northern states depending on which

pollen it is. And those are just very complex things that do need to be thought out.

Then with the chamber studies, again, that is a statistically rigorous thought process when considering it. It's an industrial engineer question almost which statisticians and industrial engineers are -- it's very similar. But to think about where you are setting and making sure that in that environmental chamber, that one that has 360 people, that there is not a blowing area. Like I'd bet you there are some of you in this room uncomfortable because it's blowing on you and some of you who may be a little bit more toasty because it's not blowing on you. And this is probably a little bit larger than a 360-person room, but nonetheless, that can have influence, and you want to as you consider those things think about those subtle things that may have influence. But thank you.

DR. HAMILTON: Excellent. Thank you very much. Good. Before we go to the open hearing, I have an announcement that I'm required to provide to you about the open public hearing session: "Both the Food and Drug Administration and the public believe in a

transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee, the FDA believes that it's important to understand the context of the individual's presentation. For this reason, the FDA encourages you the open public hearing speaker at the beginning of your written and/or oral statement to advise the Committee on any financial relationship that you may have with any company or with any group that is likely to be of impact on the topic of this meeting.

For example, financial information may include the company or the group's payment for your travel, your lodging, your expenses in connection with the attendance of this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do or do not have any financial relationships personally.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking, but it is encouraged."

So with that, we have four presentations today. Each will be limited to 10 minutes, and they'll be a brief interaction between the participants and the Committee following.

I'd like to begin with Dr. Steve Durham, who will be representing Circassia, Ltd. Thank you, Dr. Durham.

DR. STEPHEN DURHAM: Good morning, and I'd like to thank Mr. Chairman for the opportunity to address the meeting during this open public debate. My name is Stephen Durham. I am an allergist and also Head of the Section on Allergy and Clinical Immunology at Imperial College, London. I'm practicing allergist. I do clinical trials in allergy and have a special interest in immunotherapy over many years.

If I could just show my disclosure statement. I have received consultancy fees from Circassia, from ALK Abello in the context of studies of immunotherapy. I've also received lecture fees from ALK Abello. I have received research funding from ALK Abello and Novartis for immunotherapy trials through Imperial College, which is my institution, and I'm a member of

the steering committee of the Immune Tolerance Network in U.S.A.

And I'd like to acknowledge Circassia, who are a vaccine company developing a portfolio of peptide immunotherapy projects. I do research for Circassia, but I have consulted with Circassia, and I'm very pleased they give me the opportunity to speak today.

Now there is a real clinical need for immunotherapy products. This is not a trivial disease. Allergic rhinitis, as many of you in this room will know, there is an unmet need. Some 60 percent of patients are either poorly controlled or not controlled at all with current medications. The availability of immunotherapy products is such that we can demonstrate improvements in clinical outcomes at least in the same ball park as that we see with pharmacotherapy. But unlike what's available, steroids and antihistamines, these products have the potential to induce long-term disease remission; in other words, they're disease modifiers.

And just to throw up a flag for you here, this could potentially justify a smaller level of treatment

effect versus pharmacotherapy as a clinically meaningful treatment effect for a treatment which has the ability to have long-term benefits.

Allergic immunotherapy has required the title of vaccine. Of course, very importantly, this is a therapeutic vaccine. It's not a prophylactic vaccine. And whereas in prophylactic vaccine studies we're very focused on the confidence intervals above a defined clinically meaningful treatment effect, which is the current gold standard, but there are clearly differences. We're talking here about healthy individuals, a disease instance which is low in the population studied; the scoring for the disease may be typically binary; they either get an infection or do they not, or an outcome or not. And in addition, the nature of the trials themselves are very different. So it may not be the optimal way to model an allergic rhinitis trial.

If we look at immunotherapy, these are given to patients with disease. The disease incidence is high, not 100 percent; as we've heard, the pollen count may actually be low during a particular year. But

scoring is with continuous variables usually symptoms scores, as we've heard, and critically depends on the level of allergen exposure. The standard deviations that we see are large in these studies. It's not like an antihistamine trial where you recruit somebody in with a score of 9 out of 12 and follow them up at 2 weeks. Here we're following patients up for 4 months, and for much of that period, they may not have symptoms. And so we need to focus on allergic rhinitis trials in order to model our strategy in relation to the immunotherapy trials.

Intranasal steroids are the mainstay of treatment. They're licensed -- I think I'm correct in saying this -- on the basis of two significant Phase III trials with the p-value less than .05, and we've all heard very clearly from Tammy the reservations that on has relying on just p-values.

But what's interesting is if we look at the main treatment effects -- and I'll show you this -- the main treatment effect for intranasal steroids and antihistamines is around between 8 and 18 percent with a confidence intervals between 3 and 12 percent.

The point is that despite this apparent low treatment effect and wide confidence intervals I think there are a few of us in the room that would question the fact that actually antihistamines an intranasal steroids may have good clinical benefit in these patients. Many of us benefit from these treatments. It's just jolly difficult to show big treatment effects. I'm not sure why this is, but I think we need to think about what we accept as current gold standard for treatment, symptomatic treatment, and this is really what we're looking at for the immunotherapy.

Of course, there are a few head-to-head comparisons, but there are meta-analyses comparing immunotherapy with current treatment -- I'm sorry -- these are individual meta-analyses now where we look at the value of subcutaneous immunotherapy for seasonal allergic rhinitis, sublingual immunotherapy for seasonal allergic rhinitis and a separate meta-analysis looking at the effects of all the studies for intranasal mometasone furoate, which is a post-intranasal steroid which has been shown to be effective in treating allergic rhinitis.

If we look at the standardized mean differences in these meta-analyses, two of these are Cochrane meta-analyses involving many thousands of trials, large patients, large numbers of studies. Interesting, if we look at the effect size, the standardized mean difference here, and the confidence interval for the intranasal corticosteroids, it's rather comparable to that observed for the recent publication for my own group, which is a Cochrane meta-analysis .49, and these are the confidence intervals. The effect size seems to be bigger with this for subcutaneous immunotherapy compared to placebo, but on the other hand, the confidence intervals are much wider, suggesting the wide heterogeneity that one sees in these trials on fewer patients.

So how can we compare the benefit we see from pharmacotherapy trials for that in the immunotherapy trials? For intranasal steroids and antihistamines, these, unfortunately, it's difficult to get a handle on the information because they essentially report it; and in the U.S. information that's provided, in the information for the individuals study drugs, it's

provided as baseline effects and changes from baseline.

So, for example, in this study of fluticasone fuorate, which is an intranasal corticosteroid, we have the baseline effect and the change from baseline. So it's very difficult because if we look at immunotherapy trials, of course, we very often don't have a baseline year, so we only have a posttreatment value. So what we have to try and do work out a posttreatment value for these intranasal steroids and antihistamine trials. And we've done this for some of the large published trials.

And what we've got here is the baseline mean score for active and placebo treatments. Then we've got the change from baseline. We've attempted to calculate the posttreatment score by subtracting the change from the baseline, and then to work out the treatment effect -- and in this illustration, we take the delta value for the active drug and subtracted it from the delta value from the placebo drug and expressed that difference as a percentage of the placebo effect. This is the score of the placebo posttreatment. And if we do these for fluticasone

fuorate, which is a potent new intranasal steroids, we get an effect size of 18 percent.

And if you looks at the registering product studies here, two here for fluticasone fuorate; two from mometasone; and two for an accepted antihistamine, desloratadine. Then when we look at the treatment effect here, it varies between 8 and 18 percent. For the two studies for which the confidence intervals are available, we can express this as a percentage, and we see that it's 12 percent and three percent. So here we have an effect side of between 10 and 20 percent and a confidence intervals between 3 and 12 percent in two of these trials.

Now the WAO guidelines published suggests -- they recommend empirically a 20 percent treatment effect as the clinically meaningful effect. But actually if you look at this publication, it really is very empirical. It's based on the finding of a meta-analysis looking at intranasal corticosteroids and antihistamines compared to leukotriene antagonists. And if we look at the effect sizes as published in the meta-analysis used by the WAO, we can see that the

effect size for leukotriene antagonists is 5 percent. And when we look as that versus placebo and if we look at the effect of antihistamines compared to leukotriene antagonists, it's 2 percent; and for topical steroid therapy, it's 12 percent compared to leukotriene antagonists. And look at these confidence intervals; 3 to 7 percent; naught for 5 to 18 percent.

The three studies I've shown you as we've attempted to extrapolate this data we can see that the effect size for the antihistamine is either 8 or between 8 and 16 percent; for mometasone, it's been 10 and 16 percent; for fluticasone fuorate, it's between 10 and 18 percent. And here we have the confidence intervals available -- excuse me -- this is the lower bound of the 95 percent confidence intervals for these measurements, and it's 10, 3.2, 18, and 12; which is really very surprising because certain in clinical practice, we think that these drugs are very effective.

As Dr. Rabin pointed out, the effect size in recent adequately powered immunotherapy trials suggests an effect size of round about between 20 and 30 percent, round about 25 percent as he states. And this

is when we look at the difference between the active and the placebo treatment groups, and you can also derive from these studies the lower bound of the 95 percent confidence interval when you look at the numbers. And this is real data: The numbers of patients that are in these trials.

So in the studies that are published, as it were, and on the basis in Europe of which some of these products are registered, we're talking about an effect size of 25 percent with a lower confidence interval of between 5 and 15 percent, 20 percent on one occasion.

And one can do a theoretical calculation if one assumes in the placebo group a score of 7 and one assumes a standard deviation of 4.3 and a real treatment effects of 25 percent. Excuse me, just to move this one. And you can see between 7 and 5, and this is the difference here, and this is the mean effect of 25 percent. Then as we actually modify the 95 percent lower bound of the confidence intervals, obviously the closer it become to the mean then the higher the number of subjects that we need per group to establish a meaningful difference.

And you can see here that if you are to use that 25 percent to have a threshold for the lower bound of 20 percent, we'd need 3,000 per group, which is clearly not feasible.

So my concluding remarks, if I may, make some concluding remarks, my view is that there is no basis for accepting the WAO recommendation that a 20 percent reduction in means Simpson scores is the clinically meaningful treatment effect. And I would question whether one should base the 95-percent confidence intervals for the lower bound on this same value.

And my main reason for suggesting that is because if one looks at antihistamines and intranasal corticosteroids these would never have been registered on the basis of requiring this sort of rigorous requirement. If you set the lower confidence interval at 20 percent, would require 3,000 subjects per group.

Secondly, clearly, as an elegantly showed, we should not consider the confidence interval in isolation of the mean treatment effect.

And just summarizing for you, the mean treatment effect for intranasal corticosteroids and

antihistamines is between 8 and 18 percent. The limited data that we have on the lower bound of the confidence intervals in these trials for intranasal corticosteroids and antihistamines is that it varying essentially between -- you can see here -- essentially it's varying between 5 and 15 percent, and the confidence intervals we can see here is between 3 and 12 percent in these trials where we're getting an effect of between 10 and 18 percent.

Now unlike steroids and antihistamines, the immunotherapy has the potential for long-term benefits after discontinuation, which is why many in this room are very enthusiastic about developing safer and more effective therapeutic vaccines for allergies.

And if we look at the data that I've attempted to extrapolate from what's in the public domain, you can see that the treatment effects are similar to antihistamines and intranasal corticosteroids; that's 10 to 15 percent with a lower confidence interval of round about 5 percent, which seems to be justifiable if we look at actually the number needed to treat here already, clearly, these are really very high number.

So thank you for being able to make those few observations.

DR. HAMILTON: Thank you, Dr. Durham. So our next presentation will be by Dr. Peter Creticos.

DR. PETER CRETICOS: Thank you. And I do appreciate the opportunity to address the advisory panel of the FDA on allergen immunotherapeutic products.

I think many of you know I'm an Associate Professor of medicine in the Division of Allergy and Clinical Immunology at Johns Hopkins School of Medicine. And this past year I've actually changed to a part-time position there so that I could work with some of my former fellows and develop a research program in this Mid-Atlantic region.

With respect to what I should cite, I am a consultant to Merck/Schering-Plough, Greer, Curalogic, all of whom I believe are in attendance at this meeting, and I'm involved with clinical trials with Merck/Schering-Plough and Greer right now with respect to immunotherapy.

Perhaps one of the things I think that's

important here is that during my 30 years in clinical investigations I've had the privilege to study and evaluate a number of constructs, and really talking today, I'll be under the visage, if you will, as a clinical investigator involved in design, development, and conduct, and I'm not here on behalf of any particular company at all.

I think Steve has made an important point: With our increased understanding of inflammatory pathways and our knowledge of airway remodeling and genetic determinants of molecular mechanisms, what we have here is the opportunity to work with companies, to work with governmental agencies to look at novel therapeutics that have the potential to modify the disease process, induce disease remission.

My research work through the years with my mentor Phil Norman in particular and Franklin Adkinson, Bob Hamilton and others at Hopkins has been through the spectrum of looking at standard classic aqueous immunotherapy to peptide, the work we did a number of years ago, obviously to a variety of adjuvants and most recently to work with oral agents, both in terms of

sublingual tablets dissolvable as well as aqueous as well as liposomal approaches.

I purposely decided not to show slides. We were all together in Sicily actually for a symposium on specific immunotherapy, and I talked about what are the components that are important with the successful design of clinical trials, and I just wanted to emphasize a few of those right now.

I think Dr. Massie stole my thunder because the key point here is the complexity of performing seasonal and perennial studies of allergen immunotherapy, and they're highly impacted, as we have heard, by geography, patient and site selection, and of course, study design criteria.

And in the context of geographic factors, I would just point out a few thing that we've alluded to. Weather patterns including seasonal storms can completely run a clinical trial. Pollen seasons can vary as we've seen, yes, particularly with tree and grass, which are perennial plants, where the vagarities of the winter can dramatically impact upon the lack of a season or an early, robust season.

Even with ragweed, an annual plant, which is really dictated by heat, light, and units and is pretty much the same within the context of defining a season, we can see dramatic effects not only with what was presented by Ron with Walter Reed's nice evaluation of 10 years, but you might remember the volcano in the Philippines about 10 or 12 years ago put an ash cloud into the stratosphere which lowered pollen counts along the Eastern Seaboard for three full season, about 30 percent lower than expected. So these are factors that really do impact upon clinical trials design.

But perhaps most important for clinical trials is looking and carefully characterizing patients, selecting patients based on their history, their skin test sensitivity, and a variety of tools that we have that allow us to better understand that patient right now as opposed to past history, last season what did I use, and that's where nasal challenge does become very important. And certainly we need to carefully consider confounding allergens.

One of the things I've learned is my mentor Phil Norman left Kansas and he never went back, and you

kind of wonder why. Because in Baltimore he found an area where you could do very well-defined clinical trials with ragweed; the grass season is over; the mold season doesn't start until the leaves fall, so he had a very clean season to look at.

Furthermore, I think with the tools that we helped developed at Hopkins, Bob DeClaro (ph), myself, etcetera, we used skin test methodologies that we think allowed us to better identify patients, looking at not just wheal but looking at erythema, defining cut points to select patients that are more skin-test sensitive both based on intradermal titration but also based on looking at some of erythema based on a prick-puncture test to better identify people that are more likely to exhibit symptoms during the pollen season, and it says clearly that study design is critical.

We also cannot overlook the fact that nasal challenge allows you to define patients right then and there who are symptomatic. So these tools do allow you to do natural exposure studies, if you will, more effectively.

Confounding allergens, of course, is a real

factor, and we've seen that with some of the grass studies not only in the context of trees that are in the area at the same time that the relevant grass is pollinating but also confounding grasses that are not members of the temperate family; i.e., Bermuda, Johnson, that become particularly problematic with respect to look at studies where we do need to have patients from a wide spectrum of the country in order to get a good feel for whether that therapeutic agent is effective or not.

I did go back and I looked, and I think Stephen has pointed out very nicely the differences between certain therapeutic agents symptomatic on the one hand versus placebo, even controller drugs versus placebo, and what we expect to see, 5 percent, 7 percent, 12 to 18 percent. But, of course, the key point here with immunotherapy we have the opportunity to alter the disease process. Now that has a risk/benefit that we cannot overlook in terms of what we're trying to accomplish with these studies.

But I will say that I went back and I look at our clinical trials, the Hopkins experience, what I

published in 2007 in the JCI, and looking at all those studies that were initially done by Phil Norman and Larry Lichtenstein and then the subsequent group as we expanded, the first studies were co-seasonal; and what they were able to demonstrate was about 30 to 35 percent improvement versus placebo.

Our subsequent clinical trials with sKIT, we consistently were able to show improvements of about 35 to 40, sometimes 50 percent better versus placebo. But what you really have to take into mind is these were very small numbers of patients, typically 20 to 30 patients in a particular treatment arm. So these patients were very well characterized, as I alluded to, history, physical, skin test criteria that were set high. Our mean skin test reactivity was about 74 mm. These are very highly sensitive patients with respect to ragweed. We have a clean season where we see a reasonable pollen, a moderate ragweed pollen count in the belt; not as high as you see in the North or into Canada, but those have negative factors sometimes too. If you're trying to show whether something is good, you might get completely washed out on that type of a

approach.

I will point out we've discussed when you look at the clinical trials that we did most recently with the adjuvant, that is the TLR9 agonist, from Dynaback's (ph) for instance, where we were able to show 53 percent improvement the first ragweed season; 55 percent improvement the second season without any further injection. Very impressive data: 25 highly allergic ragweed patients, skin test, nasal challenge characterized.

When you then advance to a multicenter clinical trial, you did not see 55-percent means or 60, 65 percent median changes versus placebo. You saw around 21 to 26 percent. And I think this, again, brings back into reality what Stephen has pointed out: We have to look carefully at the types of patients, the numbers of patients that are required to be able to provide reasonable estimates and power calculations.

We also saw the same thing when we did our immunologic studies with peptides. The typical improvement versus placebo was about 13 to 15 percent in the rhinitis studies with ragweed that we did. If

you did the confidence intervals in lower bounds, of course, these would be significantly lower.

So I think the key point here is we can't overlook the importance of what we're trying to accomplish, and is the FDA has a mandate, and the goal is to provide safe, therapeutic products that show a reasonable degree of clinical efficacy that would justify their approval. And by reasonable, we're talking about clinically meaningful. And indeed that means we've got to look very carefully because we're all in this for the very same reason, both from regulatory, from industry, and those of us that are particularly keenly interested in clinical trial development and design. We're trying to bring advances that improve the safety, the quality of life, and the effectiveness for the health of medicine, if you will, and the well-being of society. So that's all I wanted to state. Thank you.

DR. HAMILTON: Thank you, Dr. Creticos. So next we will have a presentation from Dr. Tom Holdich from Allergy Therapeutics.

DR. TOM HOLDICH: Thank you. Good morning,

everyone. First, I'd like to thank the organizers for the opportunity to address the Committee. My name is Tom Holdich. I'm the R and D Director at Allergy Therapeutics based in the U.K. I am a company employee, but I'm not a shareholder.

As many of you may or may not be aware, in just under a month's time is the anniversary on the 10th of June of the publication of Leonard Noon's paper entitled "The Prophylactic Inoculation Against Hay Fever," and that was the first publication, the initiation of allergen immunotherapy using allergen extracts. So we have nearly a century of use now of allergy vaccination, and from that, we know that it works.

In 2003, as Steve has mention, the Cochrane collaboration did a review of papers of sublingual immunotherapy and highlighted 78 potentially relevant papers of which 33 had detailed assessments. In 2007, again, the Cochrane collaboration reviewed the paper for subcutaneous immunotherapy, and here found over a thousand potentially relevant papers, of which 275 had detailed assessments and 51 satisfied the inclusion

criteria.

However, if you look at the experience of allergen immunotherapy over its first 95 years, it is perhaps surprising limited amount of clinical evidence available. And if you unpack these two reviews, you'll find that the conclusions on the sublingual basis are actually based on 14 studies, a median size of 31 patients and median date of 1999. If you look at the 2007 subcutaneous review, you'll find the conclusions are based on between 13 and 15 studies, again a median patient size of 38 and date of 1999 to 2001.

However, in the last five years, there really has been a quantum change in the amount of evidence available on immunotherapy. Much of this has come from the study of common allergens and the use of standardized final form products.

Now just to describe those two, put you in the context, these are pharmaceutically manufactured final products to standards of GMP, good manufacturing practice. They may also be sophisticated formulations, modified allergen, depamediate (ph). There's even the addition of adjuvants. These are standardized; i.e.,

they are highly characterized in terms of the profile of the allergens and the potency of the product. There is also available data on other aspects such as stability and in-use data. They also come with preclinical data, where the immunogenicity has been studied but also aspects including chronic toxicology, genotox, reprotox, and juvenile toxicology.

So essentially, these are standard pharmaceutical products like any other pharmaceutical products; and with them therefore, there is a proposed label of the standardized conditions of clinical use, which highlights, as you would with any other drug, the patient population and contraindication and precaution of warnings but also the dose regimen, the frequency, the duration of the initial titration and the maintenance course is well defined in the label.

Most important, over the last five years, there has really been a quantum change in the amount and the quality of the clinical data has come available. This is efficacy and safety data which pertains to each of these individual products and their labeled use as stated above, and this really comes from

global Phase III studies.

So when we're now talking about this era of global Phase III studies, what do we really mean? Well, by Phase III, we're talking about double-blind randomized controlled trials. These are large confirmatory studies. They are pivotal for efficacy and safety. They'll usually set in the natural setting. These are the field studies that we talk about, and they have relevant clinical outcomes, and they essentially get regulatory review and approval. So this new methodology provides us with internal validity of the data.

In terms of global, many of these studies, in fact all of these studies, are essentially multicenter trials. Many of them are international, and they may be transcontinental involving both North America and Europe. So these are large, varied patient population. What this globality is it provides to us external validity of the data.

We have conducted some of these large field studies, so I'd like to relate to you some of the issues that occur in them, of field studies in

practice. What does global Phase III actually means? Well, as I say, large international, multicenter Phase III studies.

So again, unpacking that, large studies require a lot of patients, and these are not the type of patients that Dr. Creticos was referred to, highly selected from the investigative database. It often requires the recruitment of patients essentially off the street with media campaigns. It's a very varied patient population. They may have many other sensitivities. They may have different allergy histories.

With the international multicenters, there will be differences. The obvious one is in pollen counts, which we've talked about, and the look of the pollen season, the duration of the pollen seasons, and the intensity and the shape of the pollen seasons will be different depending on the geography. The types of pollens that patients are exposed to will also differ, different species, maybe different allergen expression in the pollens, and also, as we've mentioned before, different concurrent pollens.

Environmental there will be great differences across these international multicenters. Externally, obviously, the climate and the weather; but also internally, people's behavior, air conditioning for instance.

Again, these international multicenter, treatment practice is going to vary throughout the geographical scope of your centers. The selection of patients, even though you have very tight, rigorous inclusion/exclusion criteria, the selection of patients may be different. The expectations of the patients and the investigator may be different. The experience of treatment, the experience of the symptoms and the threshold, for instance, to initiate relief medication will be different.

And then in running these international multicenters studies, there are different regulatory ethical requirements and restrictions, for instance, in the availability of approved relief medications.

And then finally in considering Phase III was, I mentioned, here we are looking to study clinically relevant study outcome, and that means real life

measures, symptoms scores essentially of the patients. And therefore, if patients are recording their symptoms, that injects a subjectivity as opposed to some laboratory-objective parameter.

And these studies require essentially self assessment, usually on a daily basis, usually for long periods of time; and therefore, that introduces an issue of compliance and the reliability of the data.

However, there are some advantages such that in the real relevant clinical outcomes you may be able to assess other things such as the impact of the disease and the treatment on quality of life.

But essentially, we don't live in a homogenous world. We live in a heterogeneous world; and with these global Phase III studies the validity, the external validity, we're looking to achieve introduces heterogeneity into the data. From a pharmaceutical company point of view, we are looking to run these studies the first point of reference is regulatory guidelines, what guidelines are there to guide you to how you might run these to an extent for standards by regulatory authorities.

There is an FDA guidelines by CDER drafted in 2000 which has some information on the -- particularly the assessment of symptoms. More recently though there was a European guideline in 2006 specifically looking at immunotherapy for the treatment of allergic diseases. Just I've highlighted some of the elements here. They advocate the use of randomized, double-blind placebo controlled studies looking for superiority. They look to find suitable patient populations in the admission criteria. They touch on this interesting issue on run-in or a baseline period, which they say is preferred whenever possible. But except for pollens, it's variable from seas to season, and really the gist is in trying for patient selection rather than outcome assessment.

In terms of outcome assessment, they advocate the primary endpoint should be a symptom of medication score where they say that the symptom score is generally accepted, the methodology for doing that. However, for medication score, there is not validated score that exists, and in fact there are various different methodologies. And they propose that the

symptom medication score, if it is the primary end point, should be supported by other analysis, particularly the advocate a responder analysis.

Now, of course, if you don't have a baseline to compare the change from baseline, it's not possible to do a true responder analysis; and therefore they suggest a kind of lower threshold where patients can be regarded, for instance, described as well patient can be a surrogate for responder analysis. But they also consider other approaches such as days with symptom control; otherwise, known as well days.

They do, however, again, I think rightly insists that the analysis, the parameter you're going to measure and the analysis you're going to do needs to be prespecified and justified. And they do say that the clinically meaningful effect needs to be defined. However, in the guideline, they do not make any attempt to define a clinically meaningful effect.

Looking at the clinically meaningful effect -- and I'd like to commend Dr. Massie's presentation of statistics to essentially nonstatisticians, and I absolutely agree and support that statistical analysis

will provide insight into the characteristics of the data and the reliability and the robustness of the information and the conclusions that you draw from it.

However, I would propose the meaning of any effect is in fact a clinical judgment, and it's a clinical judgment that has many facets. It needs to take into account obviously the efficacy but perhaps various parameters in that. We mentioned earlier about whether the mean difference was the best parameter. Maybe we should be looking at the responder rates or something like that. And again, it was mentioned particularly these large studies there are many different patient subgroup that one might wish to look at.

But aside from the efficacy, or alongside the efficacy, one needs to consider the tolerable and safety in terms of putting that overall effect into context and other issues such as compliance; for instance, incomplete compliance will affect the treatment/benefit ratio. And then finally, the place in treatment, the uniqueness of any particular treatment where you're considering the efficacy and

tolerability.

So essentially, the meaning of an effect is a complex clinical judgment that cannot easily be adequately encapsulated in a single standardized statistical criteria. It should be seen within the holistic benefit/risk of each individual product.

Now coming back to field studies. They are obviously important to show that a product is effective in the real world. Because of the heterogeneity, they are really not good to show how well it works. So there is, I believe, a better need to define efficacy with improved methodology. So the question being raises is can that be achieved by the use of the environmental challenge chamber.

Well, in our view, the challenge chamber can seek to address many of the issues one encounters in doing the large Phase III field studies. For instance, the baseline assessment really not in a field study; however, it's essentially standard practice in an environmental chamber and can be used for two reasons. Firstly, the assessment of eligibility of patients that they do have moderate to severe disease and are

suitable; but also, secondly, you can then measure a change from baseline therefore standardizing against differences in the baseline between the groups.

Obviously, the issue is mentioned in the field studies about the pollen exposure, the intensity, and the overall environment issues patients are in are implicitly addresses in the challenge chamber, where the exposure is predetermined and standardized and also the conditions with the exposure chamber are also standardized.

The issue of concurrent pollen exposure can be a big problem in running field studies. However, it can be excluded in pollen challenge chambers, where you are controlling the exposure and you can time the studies so that they're out of the other pollen season.

DR. HAMILTON: You have one minute, one minute please.

DR. TOM HOLDICH: Okay. One of the big issues we have found in running the field studies is low symptom scores, surprising low symptom scores when you're looking at the seasonal assessment. And it led to the question of whether these are generally moderate

to severe patients. Well, in the pollen challenge chamber, if the reason for that is poor pollen exposure, then you can guarantee that. You can also run a prospective baseline to include the patients to make sure they are moderate to severe.

Relief medication scoring, as I mentioned, is an issue in field studies. It's not an issue in the challenge chamber, where generally you prohibit the use of relief medications.

The placebo effect is something we're all wondering about. A challenge chamber will not necessarily address that; at least, it can be quantified in the challenge chamber.

And then finally, the primary outcome, you can measure the change from baseline, and you can measure important things such as responder rates and look at them against or alongside the average score.

So really, a pollen challenge chamber, let us remember, it does, however, involves real patients and real pollen and recording of real symptoms but provides better control of extraneous factors, and therefore you can argue is essentially better size.

In conclusion, then I would just like to say we welcome and firmly support this initiative by the FDA and the Advisory Committee. We strongly encourage the inclusion of representation from the pharmaceutical industry and also the other American allergy societies because over the last five years we've gained a wealth of new experience in conducting clinical studies with modern products to regulatory standards, and we've have in-depth discussions with other regulatory authorities and allergists internationally, and we'd therefore be every happy to assist the agency and the Advisory Committee.

DR. HAMILTON: Thank you so much for your comments. Appreciate them. So we'd like to have the last presentation by Dr. Anne Marie Salapatek from Cetero Research in Canada.

DR. ANNE MARIE SALAPATEK: Good morning still? Good morning. My name is Anne Marie Salapatek. My disclosure is that I am the director of research and development at Cetero Research. Cetero Research is a clinical organization, and I thank also the organizers to give us the opportunity to present to you our

thoughts and our experiences and the benefits of the environment exposure chamber model in antiallergy medicine development.

We've also obviously collaborated in many, many studies with many Pharma and biotech throughout our time, too numerous to mention here. However, specifically, there'll be some examples from work collaborated with Alcon Pharmaceuticals, GSK, U.K., as well as CyDex Pharmaceuticals.

Cetero is a clinical research organization as I mentioned. Our specialties are in early-phase research. We have many, many clinical bed spread over five clinical sites and two bioanalytical labs, collectively 30-year-plus of clinical experience. But why we're here today is to tell you about our experience in allergy and asthma that might be helpful toward some of the questions that were raised this morning, important questions.

We've done over 50 environmental exposure chamber studies, many over 10 large multicenter allergy studies, so there're field studies as well, and have participated as sites in many multicenter studies as

well and impact of being involved in the development of many of the mainstay antiallergy drugs that are currently on the market as well as some of the immunotherapies current being tested.

We have six environment exposure chamber facilities, which are validated to be spatially uniformed as well as temporally uniformed over the course of their exposure, and we utilized these to great effect in the safe development of drugs, immunotherapies, and devices over our years. We've used them to test many therapeutic indications, importantly allergic rhinoconjunctivitis, seasonal and perennial, with cat and dust mite chambers, but also some of the other indications that you see here including dry eye syndrome.

There are considerable benefits what we would like to mention today to the utilize of the EEC model and many of them have been mentioned this morning already, particularly better controlled allergen exposure, ability to do studies in and out of season. But the additional important benefit that come out of the utility of this model includes all of those high-

quality hopes that we have for our clinical trials including high precision, accuracy, and the clinical relevance of the clinical outcomes that we get utilizing this model.

Furthermore, we also use this model very efficiently, as mentioned earlier as well, in proof-of-concept studies where we've combined pharmacokinetics and pharmacodynamics to actually work out the safe and reasonable and right dosing regimen to be tested in Phase III.

Again, many of the advantages have been well-recognized and have been mentioned here, but I would underscore particularly a few of them. One is because of the controlled natural allergen exposure we can better screen our patients, so these patients actually are patients that have symptoms, the signs and symptoms and allergy. This is extremely important to the discussion of whether these symptoms are due to some psychological effects of being in the same room. That cannot be discounted. However, we do know that there are about 30 to 40 percent of people who have positive skin prick test for a particular allergen of test in

the EEC in fact do not reach the symptom level that are needed in the chamber or that are predescribed or preset.

Therefore, in reality, not all patients that go into the chamber are getting symptomatic. We can utilize this to make a faster and easier study, and importantly, we can use fewer subjects. Due to the lower variability, it allows for the routine follow-up, which is so important to immunotherapy testing as we've heard here. We utilize real-time, instantaneous symptom rating, with near 100 percent patient compliance.

Seasonal flexibility, we've mentioned, again. And furthermore, I would just like to mention that there is precedence by other divisions of the FDA, particularly Division of Anti-Inflammatory, Analgesics and Ophthalmic Drug Products, to accept EEC data throughout the development of drugs, Phase I to IV, particularly for conjunctival allergen provocation testing for ocular allergy as well as for dry-eye syndrome using the EEC.

I wanted to highlight the benefits of the EEC

giving these case studies or broad areas. The first case study comes from a recently published study in *Allergy and Asthma Proceeding*, and it covers the fact that we did two studies in two different years and different patients and were able to see reproducible response in these patients, so reproducible that we could in fact pool our placebo data and then cross-compare to our different treatments. Particularly, we showed that we could evaluate solublized corticosteroids and/or antihistamine nasal spray formulations.

And what we see here on the right is a graph, Mean Change From Baseline. Again, many of the people speaking previously mentioned that an advantage of the EEC is that you can get baseline data. And what this shows is the placebo response across two studies in the two different years conducted, and it's the time in the chamber. So what we see is that these placebo responses were not distinguishable, and even though we knew that we had conducted the study to the same protocol, we still applied rigorous integrated analyses to show that the placebo response could be pooled and

comparisons of drug response made across the two studies.

These are the results from this study. On the right, again, mean change from baseline on the Y-axis and time on the chamber on the X-axis. And what I draw your attention is the fact that we showed with the square markers here that a combination, here named CDX-313, of two major antiallergy classes, antihistamine and corticosteroid, provide improved efficacy and fast- and long-acting relief for allergic rhinoconjunctivitis symptoms compare to that of the drugs alone or administered sequentially. And this supported the further development of this novel therapeutic.

Furthermore, I'd like to point out that the EEC data, the data that came from these studies was extremely comparable to that recently published in a series of studies down here by Ratner, et al., LaForce (ph), et al., Habe (ph) (inaudible), that show a very similar response rate after a single day dosing.

I think it's very important that we do compare apples to apples when we look at what's going on in the chamber versus what's going on in the field, that we

compare a single dose to a single dose.

The second case study that I would like to share with you has been recently published in the *Annals of Allergy, Asthma and Immunology*. And it shows a collaborative parallel study which was done in a chamber in North America at Cetero's EEC as well as one down in Europe at the Fraunhofer in Germany. What we found was we tested the same combination of drugs. We tested cetirizine plus pseudoephedrine. We worked to the same protocol except with the exclusion that we primed our patients, so we had short priming sessions, 3-hour priming sessions, for 2 days consecutively prior; whereas the European chamber was not their practice to prime.

Furthermore, they used grass pollen, and we used ragweed; again, this being a test for a nonallergen-specific therapy. And indeed what we found was that we had consistent efficacy shown across the two chambers in different continents between different EEC, different patients, different pollens, different exposure levels which are specific to those pollens, in and out of pollen season -- that's another important

difference -- with and without priming.

On the left is the North America data from Cetero. We see about a 2-unit difference. Again, this is now raw mean total nasal symptom score plotted on the Y, and time in the chamber on the X with the treated applied at time 0, so you see that downswing as the patients response to either placebo or to drug. And so, again, we do see about a 2-unit difference in and out of ragweed season with priming in our case.

If we look at the European instance at the Fraunhofer, we also see a 2-unit difference in response in this chamber. So, again, in and out of season with grass as opposed to ragweed. Again, it shows that we got very similar indistinguishable responses.

One important difference was we had a higher baseline effect since we had utilized priming, and the Europeans had not. However, again, the effects size was the same.

Finally, another point to make is when one looks at data that we've had that's published both in the EEC and you look at the effect size in field trials. I give the example specifically of nasal spray

Patanase. We do see a very similar effect size both in the chamber and in the field, again, when compared after single-day dosing. Again, this toward the thought that there are no false positive. Second piece: An unpublished data. And as was mentioned earlier, oftentimes when this happens sponsors don't want to continue to the field study; but in fact we show that if you see a lower efficacy in the chamber you do indeed see a low efficacy in the field.

Furthermore, we have done a lot of work linking PK to PD. Again, I think very important to the development of drugs.

So in summary then, there are recognized benefits of the EEC model which includes controlled allergen exposure and the ability to screen patients which demonstrate adequate and reproducible signs and symptoms of allergy. This results in the ideal clinical model with reduced variability as well as improved precision, accuracy, and evaluation of the clinically relevant effect of putative antiallergy medicine. This is particularly important to therapeutics which are allergen specific having long

duration of testing may require demonstration of minimal efficacy level and have the potential for longstanding disease modification which requires yearly follow-up such as immunotherapies.

And therefore in light of these data, our conclusions would be that the EEC model offers compelling benefits that warrant examination of objective and subjective data findings from the EEC studies toward utility of EEC model in the pivotal Phase III studies for putative antiallergy medicine testing. Thank you.

DR. HAMILTON: Thank you very much for your presentation. So we've heard four really excellent overviews of the variables associated with clinical studies involving the evaluation of therapeutic drugs and also therapeutic allergenic products.

And I'd like to open up the session to the Panel for any specific questions that you might have that have been raised from these four presentations. The Committee is able to ask some questions of the participants. If there are any questions, we'll hold it to just a few questions.

Linda, do you have a question?

DR. COX: No, I didn't really have a question, more of kind of an overall comment and kind of coming as the frontline practicing allergist. In practice, what we're looking for is does the product work or not work; and then when we get to use it, we're going to see variability with our patient population. I think it's pretty well established that allergen immunotherapy works while it's being used in terms of reducing-symptoms medication, but there's a downstream effect that often doesn't get looked at, and that's potentially preventing onset of asthma, long-term cost effectiveness.

We haven't seen new products to market as long as I've been in practice, and we're hearing a lot about all of this exciting products in Europe. As a practicing allergist, it's a little frustrating that we're hearing about these good products, and yet we're still only getting about 2 to 6 percent of our patients on allergen immunotherapy, which has this long-term potential benefit.

I think for our specialty's survival I'd like

to see some newer product bring some life into our specialty. And that's kind of a personal standpoint but not a question.

DR. HAMILTON: Thank you. Yes, Dr. Riedl.

DR. RIEDL: This may be a general question to the agency. We've heard a lot about the environmental chamber exposures and their potential downside and upside in terms of drug development and bring their products to market. I guess it's not clear to me what the next step is in terms of how the agency views this because we heard that there has been some meetings in the last couple of years from specialists in the field, and understandably, there's a lot of interest from clinical researchers and industry in potentially making this more efficient to develop therapeutics.

But we've heard a lot of talk. I guess I'm not clear on what's being asked in terms of this Committee for input or what the next steps would be. This is not new technology. These chambers have been in use for 25 years or more and lots of publications showing the potential utility of this. So I just wondered if the representatives from the agency could

enlighten me as to what the path forward is.

DR. SLATER: This is the next step. This discussion that Dr. Rabin presented, with the public input, with your comments about it is in fact the next step, and this is what we were hoping to achieve.

Beyond this, we anticipate that we will have sponsors that we'll wish to include these environmental units as tool at various phases in their studies. What we're struggling with -- and we're trying to have both an internal and a public conversation about -- is what's the appropriate role for these units as tools.

I think the answer that we're coming up with is it depends, it depends on what the allergen is that's being studied, what the potential benefit is, what the risks are of studying it in the natural environment versus in the controlled environment. And what role it would play in different phases of study also depends on product development and where the consideration is both for the manufacturer and for the public health considerations.

Probably the next step, the direction that we're going to go in is we are going to take what we

learned here and what we learned from our colleagues outside the agency and work toward developing a guidance document. Guidance documents have a life cycle of their own, and it's not entirely predictive predictable. But it's our current thinking that this would be very useful for people outside the agency to understand what our current thinking is on this.

At the moment, certainly going into this meeting, our thinking was we were going to work toward developing a guidance document that would help move these kinds of studies forward by articulating as clearly as we can what our thinking is about the utility of these tools. And this has been a very helpful interaction from us so far.

DR. RIEDL: That's very helpful. So if I could just add a couple of quick comments from what I've heard. I have mixed feelings about the chambers. Personally, I think they are incredibly used probably for early phase studies because of the very efficient way to look at whether there is an effect of intervention, and they may be useful as adjunctive data in sort of Phase III studies.

However, I share some of the concerns that have already been expressed. I think one of the problems in exclusively looking at chamber studies is that they are in some ways quite artificial. I have a background in air pollution work, and we know that air pollution plays a significant role in allergy symptoms or responsiveness to allergy. And again, in a chamber, you're generally pulling in either filtered air or outside air that's probably not that polluted, so I think that you miss some things that -- as was said by Linda earlier -- that on the frontlines treating patients we want some studies that show that "Hey, this works in the real world" as opposed to just a chamber study.

So I think there is utility, but I would caution against relying exclusively on those at least until we have more data to look at those two sort of circumstances.

The only other thing I wanted to add was I heard in Ron's comments that there was concern about harmonization amongst the different chambers. My own view on that is that'll take a long time to each, and

so to wait for that as sort of the reason to delay things, I think is not wise. You all have much more experience at this than I, but it would seem to me that you set some criteria, you provide some guidance, like you said, as what's acceptable in terms of the conditions, and you have lots of experts that can help with that. But to wait for harmonization, I think is a mistake.

DR. COX: Can I just add on too. The problem with the natural field studies is say you have a new peptide, ragweed, or some product. You'd spend a year getting the study designed; you get the patient enrolled; ragweed season comes; it's a bust; there is no significant count. That year goes down the tubes. Maybe it's a 2-year study, and you get ragweed the next year, and then you compile your data, and about two or three years later, maybe you get approval. You're talking five year per new products. I'm going to be close -- no, I'm not, but wishing I was near retirement -- to get new products to market in a timely way. I would like to see some surrogate marker that we would accept whether it's an *in vitro* study like some of the

assays that Dr. Durham is working on or a challenge chamber, but that's what I'm thinking about. I agree field studies are probably the best real life, but in terms of practicality to bring new products to market, we're probably talking five years per product.

DR. HAMILTON: Thank you for your comments. Dr. Castells, do you have a question?

DR. CASTELLS: I just wanted to make a quick comment about -- maybe a more basic level, maybe sublingual immunotherapy. There is a population that we are not addressing like the children population. The children who have allergic rhinitis if they are receiving immunotherapy will not develop asthma, and Dr. Buskett's studies have shown very nicely that there are a lot of parents who don't really want to give injections to their children.

So I think would agree with Linda that we need to see other products, and I'm not really sure that sublingual is the way to go, but maybe that's what we have to do for those kids. So the children's population has not been addressed here.

And the second is what Dr. Durham has been

demonstrating to have surrogate markers for immunotherapy. Do we have any kind of diagnostics with that? Can we kind of push basic science? Because I think here we -- I'm advocating for basic science, but markers that would give us some clue and some ideas. We know how difficult it is to have patients say that they sneeze 1 or 10 times in the same chamber, so I believe that surrogate markers would be something that we need to push forward. And I commend Dr. Durham for doing that.

DR. HAMILTON: Dr. Saper.

DR. SAPER: Thank you. I think these comments have been very interesting. I have a few questions regarding what you're thinking of within a guidance document. It seems that we're all agreed up in this room -- maybe I'm overstating that -- that the difference between natural exposure and nonnatural exposure are clearly present and that there is a reason to have the nonnatural exposure -- speaking to Dr. Cox's comment -- so that you can have reproducibility, that everybody has actually been exposed even though it does not completely mimic an natural situation.

Within the guidance document, are you thinking of using environment exposure chamber as the nonnatural exposure? There are other types of systems, nasal allergy provocation testing, and other ways that you can have a nonnatural exposure, and none of the nonnatural exposures mimic actually the natural experience.

DR. RABIN: We recognize the utility of things like nasal and conjuctival exposure. The issue is is that when you get to the point of studies for licensure you need numbers, and these particular studies are really very labor intensive as you can imagine. So we focused on the chambers, the units, for that reason.

DR. SAPER: That doesn't speak to Dr. Riedel's comment about the Phase I just sort of figuring this out in smaller numbers. When you --

DR. RABIN: Oh --

DR. SAPER: -- get to the larger number, then clearly --

DR. RABIN: Yes.

DR. SAPER: -- there are.

DR. RABIN: Oh, okay. As far as earlier

studies, no we would certainly -- I'm trying to -- my memory whether or not we have in this context, but it doesn't matter. We would certainly consider studies that would support further trials with something like nasal exposure. I mean just off the cuff, if I were to receive an IND saying this is what we want to do to demonstrate that this is worth pursing further down the line, it would certainly be reasonable to me.

DR. HAMILTON: Any other questions? Dr. Grant.

DR. GRANT: Well, I've reviewed environmental units for quite a while, and I think that their utility is growing, and I think the data we've received today, the data that we -- the papers that the Committee received from the agency to review showed that it is an instrument that does provide precision and does have correlates with the natural exposure. The example given of the ragweed season that doesn't exists only runs the price of medications up for the public, and that's highly undesirable and delays further the licensure.

So I think the use of environmental units as

one means of acquiring some precision, come ideas of efficacy and in speeding up the process is to be applauded. So I strong support the agency considering it developing some guidelines for the industry. I think that's a wonderful idea.

DR. HAMILTON: Thank you, Dr. Grant. Dr. Nelson, can you comment please?

DR. NELSON: Yes, I'd be happy to. One of the things that struck me was that I would agree wholeheartedly that it should be included in the toolbox of assessment means for establishing new items and bring them to the market.

I would caution a little bit about making it an across-the-board requirement for all products coming across because I think that sets up a scenario that could be detrimental and actually delay implementation of some of the new drugs with regards to access to these units, and the cost for using these units will actually be a factor somewhere down the road.

I also think that it is a very valuable tool and can be applied to multiple different products. I wonder from those -- I do have one question for some of

the presenter or perhaps people who have used them within the panel itself. The placebo effect was listed as an ability to be monitored by these individual units. So I'm wondering what the comparison is between placebo effects within these units versus those in the real world as one of the questions.

But in general, I think that using this as one of the tools for certainly earlier phase studies and possibly some of the larger when it's feasible is worth pursuing with the caution that as you get further along in your phase number of trials, Phase III, etcetera, I think there should be guidance in the document that points toward looking at a larger and more diverse set of patients because I think you're at risk of selecting a very highly allergic or tight subgroups where the applicability to the real-world patients coming into the office won't be as great.

So for early on, your selection bias could be introduced; but for later phase studies, I think there needs to be some guidance to make sure that the inclusion criteria really does bring in real-world patients and that applicability is a lot closer.

DR. RABIN: Thank you. Just a quick comment. We would completely agree. I don't think that we had considered including it in the guidance document as some sort of a necessary requirement. It was simply -- so that was never...

DR. SLATER: But I guess one thought that you brought up I'd like to explore a little bit more because if the environmental units -- and I think Dr. Holdich was leading toward this -- if the environmental unit allow us to deliver allergen to a large number of individuals in a highly controlled manner and furthermore they allow us to monitor their reactivity in a very specific, controlled, objective manner, it would seem to me that these units should allow us to include a more diverse population of study subject than you might have otherwise.

So whereas your strategy in a natural exposure trial would be to get the most allergic individuals you possible could, maybe, maybe the hope would be with an environmental challenge you could actually ditch that part of your strategy; and, therefore, you would be able to make a statement about a more diverse

population of study subjects. I don't actually know the literature well enough to know that that's actually true, but that would be one of the things that I would hope to able to come out of this with, not just increasing the predictability of the study sequence, which of course is a very big deal, but not necessarily to us, but increasing the diversity of subjects and the number of subjects that you could include in a very organized manner and collecting the data in a very organized manner.

DR. HAMILTON: Excellent. Dr. Martin, do you have some thoughts?

DR. MARTIN: Actually, as you said that, Jay, I was wondering how you'd look up a study that did both a chamber and a natural exposure, and would you allow combining that data to increase the number of participants?

DR. SLATER: Well, maybe I'm wrong, but when you said that, I think I heard all of the statisticians in the room stiffen.

(Laughter)

DR. SLATER: Am I right? So I think there

would be a problem with combining the data, but that being said, that doesn't mean that both lines of data couldn't be utilized to support the point that's being made. In other words, I would think that -- this is maybe a mistake -- but I would think that the data could be used to support different aspects of the application. In other words, it possible I supposed to envisage a situation in which in the natural exposure trial because of the problems with allergen exposure and data collection you might have to stratify brutally to really get the most allergic individuals to see the most dramatic effects; and yet, you could then also do another arm of the study.

We haven't had any models like this in we've worked with that, but something we could talk about though.

DR. MARTIN: My use of the word combine was probably inopportune.

(Laughter)

DR. MARTIN: I didn't mean mathematically combine --

(Laughter)

DR. MARTIN: -- and I guess my mistake.

(Laughter)

DR. MARTIN: But you do have two groups of people that have a similar presentation although one in the chamber and one in the natural environment, and they would strengthen one another as you had those two groups of similar exposures together.

DR. HAMILTON: Yes, Dr. Weber.

DR. WEBER: I mentioned earlier the problems with the different thresholds for different pollens and onset of symptoms or peak symptoms, and the challenge chamber would allow you with even disregarding therapeutic interventions to establish thresholds presuming that you're doing different level challenges for a variety of patients who have more severe symptoms or less symptoms. This would provide really very meaningful information as to why the relative oomph of a whole variety of different pollens is, and so the challenge chamber would be ideal for this kind of a thing.

DR. HAMILTON: Dr. Plunkett, your thoughts.

DR. PLUNKETT: I don't think I have much to

add to this discussion. I kind of agree with all the thoughts that have been given.

DR. HAMILTON: Positive addition?

DR. PLUNKETT: Well, I mean I think it's very confusing. One the one hand, it's very expensive to do these trials; so if you put an expense into environmental chamber but you can't use that data in addition to natural exposure, I think that presents a problem. So maybe in early stages whether you trying to evaluate products, that might a good idea. You see the advantages of the expense when pollen seasons don't cooperate. We haven't addressed the expense to the companies that are doing these. You might get one shot. And if you don't get that shot, then that's it for that product, so that's all I have.

DR. HAMILTON: Good. Very good comment. Sandra, would you comment please.

MS. FUSCO-WALKER: Yes. I have to echo everybody's concerns about weighing both ways of studying patients. We do live in a real world, and we have a disease that reacts to the environment, and a variety of I don't know how many people out there that

have only an allergy to one things.

However, what I'd like to also mention is there is a benefit to patients not about new products being developed, but there's a benefit to the natural field study because patients learn about their disease over that time period, and it's how our organization can to be was that our president was involved in a long-term study that actually helped her managed her child's disease because she was able to be educated over the time that she was in the study, and that's how Anma is here 25 years later and patients like myself came to be, and our kids are controlled.

So there are advantages and disadvantages, but that's a benefit from patients that I think is hidden and people don't really say. Thank you.

DR. HAMILTON: Thank you. Any more questions related to the exposure chamber or the statistical issues? Dr. Nelson.

DR. NELSON: Just one quick comment following up on Dick's comment on threshold. These units offer the potential for identifying those thresholds to Jay that's extremely valuable. And I would also urge

additional study in the area of looking at longitudinal exposure to pollen; because as we treat patients, we're treating patients through a pollen season and not a pollen event. So translating and doing those correlations studies that look at duration of exposure as well as volume exposure over a period of time, not for each individual antigen because that's certainly not feasible at all. But doing that in a couple of pilot cases to show that "Yes, it is indeed a surrogate measure that can translate into an entire season of pollen.

DR. HAMILTON: Dr. Self, I'd like to ask you to comment on Dr. Durham's presentation with regard to the questioning of the 20-percent target placed on steroids and what you thoughts are on that.

DR. SELF: Well, I found that enlightening. I didn't know that that's where the margins were set. I guess my main reaction was that since the two classes of products are addressing similar issues that having different thresholds for clinical significance doesn't make sense to me that the prospect of longer term effects by some of the immunotherapic reagents sounds

like that's an area that should be addressed more specifically. So that to me argues for trials that would go longer than a single season to document that effect. If that's really distinguishing these two classes of products, then that's I guess where I would go.

The other thought I had, back to the controlled chambers, is it's a perfect setup for a proof of concept sorts of studies and all of that. I think it's certainly not a replacement or a surrogate based on everything that I've heard so far with natural exposure field trials.

But one thing that has occurred to me when we talked about delivering different doses and different levels of challenge and perhaps more diversity in the population of subjects that could be studied would be really important information for the design of those field trials. So I think there's some efficiency that could be had in doing that larger, perhaps longer field trials based on the data generated from these chamber studies. So that was something that occurred to me too.

DR. HAMILTON: Thank you very much. Any other comments?

(Pause)

DR. HAMILTON: So, Gail, what about lunch?

(Laughter)

DR. HAMILTON: So let's break for lunch. We'll be coming back at 1:30.

(Recess)

(Off the record)

(On the record)

DR. HAMILTON: We're back after lunch. This afternoon we're going to focus on Topic II, which deals with the research overview. We'll begin by having a presentation on the overview of the research program of the Center for Biologics Evaluation and Research by Dr. Carolyn Wilson. Dr. Wilson.

DR. WILSON: What I'd like to do for you today is to provide an overview for our site visit process and a little bit of information about our center in general and our approach to our research programs and now it fits into our regulatory mission so that you can understand why the site visits are so important.

Our vision for the center is to use innovative technology to advance the public health, so we're looking at both public and individual health in the U.S. as well as globally to facilitate development, approval, and access to safe and effective products and promising new technologies and to strengthen CBER as a preeminent regulatory organization for biologics.

Our mission is to ensure safety, purity, potency, and effectiveness of biological products including vaccines, blood products, cell, tissues, and gene therapies and also not explicitly mentioned but as I'm sure you know also allergenic products for prevention, diagnosis, and treatment of human disease.

We have a variety of complex products that we regulate, and I know you're obviously familiar with the one down in the corner, the complexity of regulating allergenic products. In addition to that, we regulate obviously preventive and therapeutic vaccines, all the blood-like components and derivates, novel therapeutic approaches including cell and gene therapies, xenotransplantation products, all human tissues and various related devices. So we have a very broad scope

and a huge public health impact as you can imagine with the types of products that we regulate.

We have recently identified our strategic goal as part of the process that the FDA is going through in terms of strategic planning, and the first is to increase national preparedness to address threats from bioterrorism, pandemic, and emerging infectious diseases, improve global health through international collaborations, enhance ability of science and technology to facilitate development of safe and effective biological products, ensuring the safety of biological products, advancing regulatory science and research and managing for organizational excellence. And obviously the one relevant to our research program is to advance regulatory science and research.

Our vision for this part of our strategic plan is that our research programs show be both proactive while also being able to be responsive and ideally very collaborative as well and that the program should provide our center with the scientific expertise, the various tools we need, and the data to support science-based decisionmaking and policy development.

The way our science fits into our regulatory mission is you can imagine that as novel products are developed or applying novel technologies to existing products that these all are driven by public health needs. And as these come in, they present sometimes regulatory challenges. There may not be appropriate assays and tools in place, reference material, maybe a missing animal model that can help predict safety or efficacy.

So that's where our regulatory science program comes in through the process of both discovery, development of new tools, assays, reagents, and a number of reference materials and standards. We then can develop regulatory policies and do our decisionmaking with improved data and information. And those policies are conveyed, of course, to the sponsors, and that means that we get improved data from the sponsor, allowing us to have a better handle on how to access benefit and risk. Ultimately, the idea is that all of this would result in a licensed product that's both safe and effective and has a positive impact on the public health.

Our center is organized with seven offices. The director and deputy and associates are in the Erlenmeyer flask, and then the three Petri dishes are kind of cross-cutting offices that support all the activities: Our office of Management; Communication, Outreach and Development; and Compliance and Biologic Quality.

The four Eppendorf tubes are offices that have research: Biostatistics and Epidemiology; Cellular, Tissues and Gene Therapies; Vaccines Research and Review; and Blood Research and Review.

Our research facilities provide a variety of technologies in the form of a core facility. As you can see, this provides support for a variety of molecular and biochemical methods that scientists need. We have some limited core support for flow cytometry and confocal microscopy. We have a state of the art vivarium with procedure rooms, and it supports studies in both rodents and nonhuman primates, BSL-2 capacity; and then we have several BSL-3 laboratories, and some of them are also equipped to use animals under BSL-3 conditions.

We have a wide range of scientific expertise within the center; a number of novel technologies are represented such as experts in NMR, mass spectrometry, flow cytometry, and we're now getting more well verse in high throughput sequencing, as you would imagine, a lot of microbiology, and a lot of immunology, biochemistry, molecular biology, cell and development biology. And this broad number of disciplines provides a rich place for interdisciplinary collaborations and problem solving to these regulatory science issues.

One thing that you may not realize about our center is that we use what's call a researcher/ regulator, and what this means is that these scientists spend part of their time doing their research and another part of their time doing all the same review activities that all of our full-time reviewers would do. So this means that they're reviewing submission to the agency, they're going out on inspections, they're writing documents, they're presenting at advisory committees as you probably saw this morning, and so on.

What this means is because they're on the frontline seeing the regulatory files that are coming

in and identifying firsthand what are the gaps in the knowledge and the methods and so on that are impeding development of a certain class of products. And the other advantage, of course, is that they so see across a whole class of products as opposed to an individual product, and this allows them to then apply their research expertise to the most important problem.

We also integrate some of a top-down and bottom-up approach to our research programs. While it's very important, of course, for that grassroots identification of regulatory problems, we also want our research scientists to be doing it in a context of identified priorities. So that is a process that goes on on a yearly basis where we look internally at our portfolio of regulatory files; we do some horizon scanning to see what kinds of products are coming, what are the public health needs and from that derive our research priorities, offices drive their priorities and develop research plans. And then the research scientist themselves develop their own proposed programs in line with those various priorities areas.

An important component that happens every four

years is this external review that we get through the site visit process, and this provides additional input. Are we doing our research in the right areas? Is the research relevant? Is it of high quality and being productive?

As I mentioned, we set research priorities each year. I'm not going to read through these for you, but you have them in your handout. They cover a wide array of different topics of relevance to our regulatory mission.

As I mentioned, we have our external review every four years. I wanted to also let you know that we also go through an internal cyclic review process through the Promotion, Conversion Evaluation Committee. Once an investigator has been converted to permanent status, then they undergo this review process every four years to make sure that their research is continuing to be relevant and productive and high quality.

In addition, we have an annual review of our research program, and we use our research-reporting database where each investigator provides a progress

report of their prior year work, of their future plan, their budget request. We update it for all the various presentations, publications, other relevant output. Perhaps, there was a guidance document that was informed by data from their program, for example, and that information is review then at several levels: their lab chief, their division director, the office associate director for research, and the office director. All look at this information and rank it on the basis of relevance, productive, and quality. And then funding is allocated in accordance with those rankings.

The site visit report, which is what you're going to be looking at today, is what's called a draft, so a subcommittee of this group was tasked to come and perform a 1-day, onsite site visit. They've developed a draft report of their recommendations, and it's your task today to review that, identify whether or not any changes need to be made or whether or not it can be approved in its current form. It doesn't become final until it has been approved by the full advisory committee.

The report is very important to us. We use it in a variety of ways. We use it for this internal peer review process; also, the PIs take the comments that are provided in these reports very seriously for improving their own research program. And of course, management also uses the recommendations in their thinking about resource allocations.

Finally, I just want to thank you, and I also want to thank the site visit reviewers because this really is a critical component to our research programs to make sure that it continues to be on target and high quality and is fulfilling our regulatory mission. I thank you for your attend and happy to answer any questions.

DR. HAMILTON: Dr. Wilson, you mentioned that about 20 percent of the staff is actually a research/regulator, that type?

DR. WILSON: Uh-huh.

DR. HAMILTON: Just 20 percent?

DR. WILSON: That's kind of a ballpark figure to be honest. I think I have to go back and update that because that number could've changed in the last

year or two.

DR. HAMILTON: But both Dr. Slater and Dr. Rabin are in that group?

DR. WILSON: Yes. They're researcher/regulator.

DR. HAMILTON: Yes. Exactly.

DR. WILSON: Yes.

DR. HAMILTON: Thank you. That's good. Thank you very much, Dr. Wilson. Next, we'd like to have Dr. Konstantin Chumakov, who is Associate Director of Research in the Office of Vaccine Research and Review. Thank you.

DR. CHUMAKOV: Dr. Wilson gave you an overview of CBER research program, and I will zoom in and give you some specifics about our Office of Vaccines Research and Review because each of the three product offices are slightly different in their approach to research. One reason for our office is that we are about the size of two offices combined, so we have the biggest number of researcher/regulators, so it takes some additional effort to coordinate our research programs.

The office consists of three divisions. The first division, the Division of Vaccines and Related Products Application, is where full-time reviewers are located. There is no research program in this division, and it's strictly a regulatory staff that performs review of different applications. But two other divisions, Division of Bacterial, Parasitic and Allergenic Products and Division of Viral Products are involved in research, the scope of which is clear from their names.

So the Division of Bacterial, Parasitic and Allergenic Products contains five labs -- I really don't see it on the screen, so -- the Laboratory of Special Pathogens; the Laboratory of Bacterial Polysaccharides, the biggest lab; Laboratory of Enteric Infectious, and Transmitted Diseases; Laboratory of Microbacterial Diseases and Cell Immunology; and the Laboratory of Immunobiology, the one that you are review now, the site visit for which is the subject of today's meeting.

The mission statement for our office is to protect and enhance public health by ensuring the

availability of save and effective vaccine, allergenic products.

(Pause)

DR. CHUMAKOV: We approach to accomplishing this mission by doing three types of activities. First, we review, evaluate, and take actions on different applications that come in the form of I&Ds, BLAs, amendments. So this is the regulatory part of our mission. We also develop policies and procedures that govern all these processes and the development of new products and bring them to market.

Last but not least is that we conduct research that is related to these issues. The reason why we do this is that FDA occupies a unique niche in the pipeline of biotechnology products: We are the last safeguard on the way of new medicines and therapies to the market. So we need to study, and nobody else are in the position to conduct this type of research that really ensures the safety of products. We know more than average scientist in academia, and we know some things that perhaps are familiar to scientists in industry, but since we are exposed to different

products that are in many cases proprietary, so the FDA scientists are uniquely positioned to address certain regulatory issues that are not maybe obvious to scientists working in other environments.

One other important reason for why FDA conducts research is that the results of our studies are published in open literature, and they become public knowledge, and they benefit the entire industry and the scientists working in developing those products. So this is something that is really important to maintain high quality of research in these areas.

The purpose of our program, the reason why we do it in house is that there are certain regulatory issues that our researchers/regulators see in their daily regulatory work and the most efficient way to address some of the problems that may arise in the course of evaluation of new products is to add them on the bench, to perform some studies that would address some issues and also develop some methods and standards that are needed to evaluation of safety and efficacy of new products.

The fact that we conduct research also allows us to attract highly qualified scientists that actually are interested in maintaining their proficiency in their fields of research by conducting firsthand research programs, and it also helps us to maintain high profile on international meetings of scientists. Since our researcher/regulators are involved in themselves, the respect that they command at meetings of other scientists is higher than it would be if they would just be performing reviews. This is something that is important to maintain high respect to the agency and the decisions that are made by the agency are actually accepted easier when they are made by scientists who are involved in the research.

But we have a problem because our scope of our research and the mission of our research is very well defined. We don't study anything, but we address issues that are most important to regulatory process. But the only way to maintain high quality research program is to allow scientists to determine what they are doing, so investigator-initiated research is the universal model that proved its utility in any

environment. So the mission of our research management process is to reconcile the strict mission of our organization with the researcher-initiated model.

In our office, we established this scheme that may look quite cumbersome, but really it's very simple. Everything revolves around principal investigator who is a researcher reviewer and is an expert in his or her field, is exposed to scientific literature, goes to scientific meetings, interacts with peers, and by being involved in the regulatory process is well-familiar with the challenges in his or her field. So they come up with some proposals or program. They form their research programs also by using input from the Research Management Committee.

The Research Management Committee is the body that we organized within the office that includes representatives from all product divisions as well as from full-time regulatory division. This committee reviews on an annual basis new development in the industry and new challenges that face and communicate priorities to principal investigators. Then the program that is formed by the principal investigator is

discussed with the lab chief and with the division director, and on this way the full portfolio of projects proposed by principal investigator then goes back to the Research Management Committee that reviews the overall portfolio for completeness, for unnecessary duplication, for potential gaps and then gives back this information to investigators. Finally, this also results in resource allocation decisions that are made by Office of Vaccines in consultations with the center. So this is how our annual cycle of research planning and reporting works.

The priorities that our scientists work on are safety, efficacy, and availability of products. This is something that perhaps will never change. This is the three cornerstones of vaccine regulation.

Just to give you an idea of the scope of research conducted by the office's scientists, I will list just a few issues that they address. In the field of safety, of course, an important part of research is evaluation of purity. That includes detection of advantageous agents in vaccines, studies on cell substrates. We evaluate utility of novel scientific

technologies to access consistency of products including genomics, proteomics, and all cutting-edge methods. We also create methods and models to study potential toxic effects of vaccines and vaccine components adjuvants and so on. We determine biomarkers of pathogenicity to create new methods for assessment of safety of live vaccines. There is a special host of issues related to live organisms used as vaccines. And finally, we study mechanisms of vaccine-associated adverse events and the way to prevent them.

In the area of efficacy, our scientists study pathogenesis to indentify correlates of protection and find biomarkers that would enable evaluation of vaccines efficacy. We create methods for evaluation of immunogenicity and potency and productivity of vaccines. We study mechanisms of innate and adaptive immunity, which is critical for the ability to regulate vaccines, and we study mechanisms of action of edjulance (ph), which is also something that is very important and becoming increasingly important for new generation of vaccines.

And finally, in the area of availability, we study new methods to induce immunity. That includes DNA vaccines, synthetic vaccines, modifications of antigen in order to present them in the best and most efficient way. We work on methods to evaluate consistency of manufacturing process. We evaluate novel technology and novel platforms vaccine manufacture such as, for instance, manufacturing in plants. We work on 3-R concept -- the reduction, replacement, and refinement -- of animal test, which is very important. It's widely used in regulation of vaccines, and we work on replacement and getting maximum information from the animal experiments. And also we recently started to get involved in the regulation of probiotics, and these are new products that present their own challenges. We are studying, working in this direction.

As I described to you, after proposals are formulated by investigators, they are evaluated by their lab chief and division director, and the rating of research projects is done based on three criteria: Public health significance including all the

components, scientific merit of each proposal, as well as qualification and productivity of investigators. Each project gets rated, and feedback is given back to investigators.

And finally, resource allocation, and here is an example of last year's budget. About 40 percent of our resources in terms of dollars spent for research are coming from our internal FDA budget. And there are also these parts of the pie which pandemic influenza initiative, modernizing science initiative, and critical path initiative. There are three programs that are run by the Office of Commissioner. This is congressionally mandated spending that comes with a special reporting requirement. That's why they are not a part of the internal budget but rather are administered through the commissioner's office. Award are given at the center level. So about 75 percent of our budget comes from FDA budget.

We also have some royalties for patents that were approved to CBER investigators as well as we get some external grants. Since we do not apply for extramural grants at NIH, these grant come in the form

or interagency agreements with NIH, CDC, BARDA, DARPA, and many other agencies of the Federal Government.

Finally, the role of site visit, as Dr. Wilson already told you, is to evaluate scientific merit of the program and, most importantly, to review proposed research plans, something that we need your input on because the next site visit in the four years, and the investigators need to have an external feedback from experts to make sure that the research programs are on target and really are addressing the most important regulatory issue. Also one important component of site visit report is evaluation of personnel actions that are proposed and to guide the Promotion, Conversion and Evaluation Committee in their decisions to grant permanent tenure status to investigators and to promote them to the next grade.

And I think this is my last slide, so if you have any questions.

DR. HAMILTON: Thank you. Yes, Dr. Riedl.

DR. RIEDL: Could I just ask you a quick question. You highlighted this interesting dynamic between balancing sort of about the scientific merit of

the investigator-initiated projects and also fulfilling the mission of the agency or the goals of the agency. When you mentioned how the research programs or projects are evaluated, is the public health significance given equal, lesser weight compared to the scientific merit? Are those things sort of weighed equally or is there more emphasis put on the actual science at the cost of fulfilling the agency's missions? Could you comment on that process a bit more?

DR. CHUMAKOV: Yes. We don't have a strict numeric solution to this issue. It's not like we have a score that we have a threshold. It's more have an effect of forcing people to verbalize their decisions, and certainly, we want to have high merit and high public significance. It's clear that if we have a gap in certain type of research with a very high public health significance we will be glad to support projects even if they are not completely innovative of something. On the other hand, if somebody proposes something that can have a long-term effect on the industry itself even though there is no immediate

public health or regulatory concern, we also support this type of research just to provide a forward-looking, basically set an example for the industry. It's always a balance.

But I must say that in general, I think our research mostly -- I would say that predominantly all of our projects meet both requirements. And the reason is that for the past few years, our resources started to kind of normalized, but in the past 15 years, we are in a very, very strict budget situation. It's just a result of natural selection; only those projects that critically important and are the best survive.

DR. RIEDL: Thank you.

DR. HAMILTON: Could I ask a question. You showed very nice schematic where the Research Management Committee sort of defines the research priorities for the divisions. How does the Research Management Committee come up with ideas to propose priorities? In other words, just take the field of allergy. How do they define priorities for the field of allergy? Or do they get feedback from the -- tell me a little bit about how this interaction occurs? You

have mentioned they --

DR. CHUMAKOV: Sure --

DR. HAMILTON: -- set priorities --

DR. CHUMAKOV: -- yes --

DR. HAMILTON: -- for the --

DR. CHUMAKOV: -- yes --

DR. HAMILTON: -- working group.

DR. CHUMAKOV: The priorities are not set in the sense that we dictate to investigators what they should be doing. Basically, this committee meets twice a year. In the spring, we meet to discuss if anything happened that warrants attention that is not being covered by our research program, so we communicate it since there are representatives from all division that can take it back, and division directors are as a well a part of this committee. These priorities are communicated.

But it's more like a backup system because investigators they are expert in their own field, so they know it very well. But if our previous cycle revealed some gaps and we realize that even though there is an important prior it's not being addressed by

any investigators. So we actually make it known to investigators that this is a field that anybody who would come up with a solution would probably be in a better position to get additional resources. It's kind of dialogue, always a dialogue. It's not like the committee meets and decides that somebody needs to do such and such an experiment. It's more like horizon scanning and trying to communicate something that perhaps should be clear to investigators always but for some reason may not be covered.

DR. HAMILTON: What percent of the activities under Dr. Slater are allergy versus parasitic versus bacterial? Because he oversees all of them.

DR. CHUMAKOV: Well, I think that allergenic products are addressed by this lab of immunobiology --

DR. HAMILTON: Which you chair.

DR. CHUMAKOV: -- to investigators, and there are I think 17 investigators in the division, so it's probably maybe between 5 and 10 percent of the workforce that is --

DR. HAMILTON: Oversees.

DR. CHUMAKOV: -- dedicated to allergy. It's

a small part of the division's activities.

DR. HAMILTON: Thank you. Any questions?

(Pause)

DR. HAMILTON: Thank you so much. That was excellent.

Now we'd like to turn to the overview of the actual specific research program in the Division of Bacterial, Parasitic and Allergenic Products by Dr. Slater.

DR. SLATER: Thank you. We're in the process of drilling down on LIB so that when you get to the site visit and close session you'll be oriented as to the environment that LIB operates in, so were drilling down a little bit further to the Division of Bacterial, Parasitic and Allergenic Products. I always like to say this sounds like a division the name of which was put together by a committee, and it was the product of a merger, and in fact it is. It's the product of a merger in 1999 as the Division of Bacterial Products and Division of Allergenic Product and Parasitology. Or has Dr. Rabin has often told me, this is the division of not viral products.

(Laughter)

DR. SLATER: But the leadership at the beginning was Dr. Drusilla Burns, who's now Acting Deputy Director of the Division. She was the Acting Director for the first year and a half or two years of its existence. Then under Dr. Richard Walker took us through the next seven or eight years. Dr. Milan Blake, who passed away last summer, was in charge for the next two years, and then I became the Division Director in the past year.

This is another picture of the structure of the division. This is the immediate office of the director. I'm the Director. Drusilla Burns is the Acting Deputy. We have a regulatory staff, a total of five full-time equivalents, actually six full-time equivalents at this point.

The two largest laboratories: Division of Bacterial Polysaccharides and Division of Respiratory and Special Pathogens, with their lab chiefs indicated. Then there's the Laboratory of Enteric and Sexually Transmitted Diseases, the Laboratory of Mycobacterial Diseases and Cellular Immunology, and finally, the

Laboratory of Immunobiochemistry, which we're discussing today.

I like to show this slide to give you an idea of what our broad regulatory and research portfolio is, and what you see here is that it's broadly speaking a number of organisms that our group is responsible for, the noninvasive toxin producers, the invasive organisms for which protective responses are those to the polysaccharides and some intracellular pathogens, enteric pathogens, a parasite, and other sort of nonclassable entities such as allergenic products. And what I'm going to do is go very quickly through each of our units and show you which ones they are broadly responsible for.

The first is the Laboratory of Bacterial Polysaccharides, and you can see here not surprising that they're responsible for *H. infu*, *Neisseria meningitidis*, and *Strep pneumoniae*. They are also responsible interestingly for *Salmonella typhi* vaccine; the injected vaccine is a polysaccharide-based vaccine, and therefore from a regulatory point of view, they handle applications that have to do with that

particular vaccine. Their research activities are really focused on these organisms and related organisms as well.

And within that group, like the Laboratory of Bacterial Polysaccharides, there are six principal investigators including Dr. Willie Vann, who is the chief of that group. I'm not going to go through each of their projects, but you have them there as an indication of the breadth of investigations that are performed in this group.

Next down the line is the Laboratory of Enteric and Sexually Transmitted Diseases, not surprisingly focusing on the enteric organisms. They also have responsibility for *Salmonella typhi* vaccine, but this is the oral vaccine that they contribute to the regulation of. The organisms that are listed in parentheses are ones for which there is not a specific product but is a major focus of investigation in the group.

You'll see as well that this group has in parentheses *Staph aureus*. We have established several years ago a division of research effort into *Staph*

aureus with the anticipation that we will be seeing product submissions for vaccines for *Staph aureus*.

This group also has responsibility for submissions having to do with probiotics. This is, as you can imagine, a large, complicated group of products submissions; and in fact this lab, which is one of the smaller labs in the division, is quite busy from a regulatory point of view. Within that group, there are two principal investigators. Scott Stibitz is the lab chief. Dennis Kopecko has been with us for nearly 20 years. They, as before, have a basic program that is both broad and deep and touching on these organisms and the diseases caused by them.

The Laboratory of Immunobiochemistry is the lab that you are going to be reviewing today. I'm not going to talk specifically about their research program except to focus on just how deceptive having a single line here is; allergenic products there are at last count 1,273 allergenic products of which there are 19 standardized ones. Again, from a regulatory point of view, this is a very busy unit, and you're be hearing more about the research activities in this lab in the

closed session.

The Laboratory of Mycobacterial Diseases and Cellular Immunology focuses on MTB, *M. bovis*, *Francisella tularensis*, and malaria. Malaria is an interesting research area for us because we don't actually have a freestanding research program in malaria even though as malaria investigations come in they will be coming to us. We actually have a collaborative malaria laboratory effort with the Office of Blood Research and Review, and that collaboration has been working very well. Again, from a regulatory point of view, a very busy lab. There are three principal investigators in that unit. Sheldon Morris is the lab chief. Karen Elkins and Siobhan Cowley have freestanding research units within that group and as I said, the malaria program in collaboration with the Office of Blood.

And finally, the Laboratory of Respiratory and Special Pathogens has control over *B. pertussis*, *Clostridium tetani*, *Corynebacterium diphtheria*, and *Bacillus anthracis*. As you can imagine, a very busy regulatory unit from a vaccine point of view. They

also participate in the *Staph aureus* research program with the Laboratory of Enteric and Sexually Transmitted Diseases.

In that unit, there are five principal investigators. Drusilla Burns who is, again, my Acting Deputy Director of the division is the lab chief of LRSP. Juan Arciniega, Erich Keller, Tod Merkel, and Mike Schmitt are the other PIs in that group.

Again, this is the outline of the DBPAP unit. The presenters that were heard at the LIB site visit, which occurred a couple of months ago, were these four people. Ron Rabin, the lab chief, made a presentation. Ashraf El Fiky, and Taruna Khurana, who are staff fellows in the lab made presentations as well. And as you've probably gotten the drift of, but may not have been stated explicitly, we're under somewhat anomalous situation in which I am both the Director of the division, which is why I'm talking to you now, but I'm also a medical officer and a PI within LIB, and I made a presentation as well. Thank you very much, and I'd be happy to take some questions before we get onto Ron's organization.

DR. HAMILTON: Any questions?

(Pause)

DR. SLATER: Okay.

DR. HAMILTON: Thank you, Dr. Slater. Dr. Rabin. Now we're going to have an overview of the research programs specifically in the Laboratory of Immunobiochemistry. Thank you.

DR. RABIN: Thank you. As you can see, in preparation for the evaluation of the site visit report, this is simply a reiteration of this overview that was given at the visit in November 4.

LIB supports the regulatory mission of CBER, FDA in assuring the safety and efficacy of allergenic products through original and directed research projects, expert advice, lot release, and BLA and IND review. We were once the Laboratory of Allergenic Products, and then we were folded into the Laboratory of Immunobiochemisty into the Division of Allergenic Products and Parasitology, and then these divisions were joined.

As you well know, natural allergenic extracts are complex mixtures of allergenic proteins based

largely on selective aqueous extraction of natural source materials such as pollens, insects, etcetera, needs for diagnosis and for therapy. There are over a thousand nonstandardized products which are marketed with rather uninformative unitage of weigh/volume or protein nitrogen units/ml. There are 19 standardized products, which we've talked about at length this morning in which the unitage correlates to biological potency either by mass units, BAU, or AU or specific allergen. We control them for potency and stability. They're based on identity to U.S. standard, and while they constitute a small minority of the product number, they also constitute a large plurality at least of product volume.

We'd like to and we increase the number of standardized products, and I think we discussed that at length this morning. I don't know that we need to discuss it anymore now. Increased purity standards is something that we would like and improved characterization methods and then in addition to that, improve some of our assay methods, which I presented to you this morning.

We, of course, are aware and are current on issues of recombinant and engineered allergens. Currently, there are certainly potent research tools to dissect the immune responses and modify them to study structure and structure/function relationships, and perhaps develop novel products. They obviously give us a number of opportunities and present some challenges as well. The allergenicity is not related to immunogenicity, which is the case for a natural product or even a recombinant product that is identical to the natural product. That's a good thing from the standpoint of patient care, but obviously since we use allergenicity as a measure of potency, it does present some problems with regard to standardization as does the fact that they are unique with some unique biological features, but they do present themselves as possible standardization tools. Certainly, they can have better purity and consistency of product as well as stability and enhanced delivery systems. But the indications may be very specific in that some may be ineffective for diagnosis and only effective for treatment, and some diagnostic products for that matter

may be ineffective for therapy. So that is obviously an evolving issue.

The previous site visit, the November 2010, was in June 2006, and the Committee stated that the research was relevant to the mission of the laboratory and deserved continued support from the agency.

This has been our current staffing. Philippa Hillyer is, again, our lab chief. Philippa Hillyer is soon to be a visiting associate in the lab. Zeng Zhao is currently a visiting associate, but will soon be leaving the lab. Ashraf El Fiky joined us a little over a year ago. Jay Slater is the Supervisory Medical Officer, and Taruna Khurana is a visiting associate that works under him and basically performs and manages his research projects. We have the regulatory staff. The individuals listed here who I outlined, again, this morning. These are the regulatory duties, again, which I outlined this morning: The lot release, reference standard, distribution and maintenance, regulatory review, implementation. We haven't discussed the implementation of Category 3A product reclassification. This has been discussed in previous APAC in which we

are revaluating over 1,200 nonstandardized products for efficacy. The ISO 17025 project and the RID to ELISA project we've discussed in detail, and I guess we can give you a message from our sponsor. For all those who haven't heard, we are hosting and co-organizers of the 13th International Paul Ehrlich Seminar, regulatory control and standardized of allergenic extract, which will be in Washington, September 14 through 17. And if you wish, please email me and I'll send you a program. It looks to be a terrific concert -- concert.

(Laughter)

DR. RABIN: Well, Dr. Hamilton is on the program, and he said he was going to sing, so --

(Laughter)

DR. RABIN: -- perhaps it is. It'll be an excellent conference.

(Laughter)

DR. RABIN: Shouldn't have had that dessert, that sugar rush. The scientific goals of the lab correlate with those of the regulatory mission, the latter being with regard to allergenic structure and function. We have the multiplex allergen extract

potency assay, extract characterization, endotoxins, and allergenic extracts -- those are two of Dr. Slater's projects -- and then modifying allergic response is more relevant to my program, which is the biological activity and expression patterns of types 1 and 3 interferons and the multiple species within those categories.

The regulatory responsibilities to correlate with our research program in that improved lot release capabilities for current and future products, allergen standardization and the immunomodulatory approach to inner city asthma as well as extract safety and efficacy relate to the issue of endotoxins in the extracts and multiplex allergen extract potency, particularly the cockroach allergen standardization and then parameters of effective immunomodulation and novel approaches relate, again, to my project, which focuses on types 1 and 3 interferons.

And that's all I have to say. Thank you.

DR. HAMILTON: Any questions for Dr. Rabin? One question that I had was you had mentioned that -- are you actively involved in the reclassification of

1,200 extracts did you say?

DR. RABIN: Yes.

DR. HAMILTON: What does that reclassification represent? Or what are you doing?

DR. RABIN: Oooh. Jay -- I think I'm going to let --

DR. HAMILTON: It sounds like a very big project which --

DR. RABIN: I think I'm going to -- because there's some legal overtones, I'm going to let Dr. Slater --

DR. HAMILTON: Oh.

DR. RABIN: -- handle that question.

DR. SLATER: This is a project that is really completion of a project that was started in 1972 to 1974 with the initial efficacy review that began when biologics, including allergen extracts, were transferred from NIH to FDA in July 1972. Shortly thereafter, an expert panel reclassified all of the existing allergen extracts at that time, classified them according to a rubric of evidence of efficacy and safety.

Another panel was reconvened in the early 1980s to reclassify them, and we internally reviewed all of those to try to draw some judgment -- to come to some conclusions as to which products fulfilled their requirements based on the best current evidence that was available. Needless to say, that was a very lengthy project, and the evaluative portion of it is nearly at an end, and we'll be discussing that further in future Advisory Committee meetings.

DR. HAMILTON: Thank you. Thank you very much. Questions?

(Pause)

DR. HAMILTON: That was a very nice overview. Thank you, Ron. Very well. We are scheduled to have a break at this point, but I would propose that we move right into the closed session if that would be okay for the Committee.

DR. DAPOLITO: Can you give a minute to clear the room.

DR. HAMILTON: Oh, I have -- yes. Gail has a comment to make.

DR. DAPOLITO: I just need a minute to clear

the room.

DR. HAMILTON: Oh.

(Off the record)

(On the record)

AV TECHNICAN: Ladies and gentleman, this is a closed session. Everyone will please leave the room except for the panel members; they're allowed to stay.

(Off the record)