FOOD AND DRUG ADMINISTRATION

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ALLERGENIC PRODUCTS ADVISORY COMMITTEE

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OPEN COMMITTEE DISCUSSION

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WEDNESDAY,
SEPTEMBER 13, 2006

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The Committee met in Conference Rooms A and B, Building 29B, National Institutes of Health, Bethesda, Maryland, at 12:00 noon, Larry Borish, Chairman, presiding.

COMMITTEE MEMBERS PRESENT:

LARRY BORISH, Chairman

FRED M. ATKINS

CHRISTY OLSON

STEVEN OSTROVE

JAY M. PORTNOY

GILLIAN SHEPHERD

MARSHA WILLS-KARP

CONSULTANT PRESENT:

LYNELLE C. GRANADY

EXECUTIVE SECRETARY PRESENT:

GAIL DAPOLITO

ALSO PRESENT:

JAY E. SLATER

RONALD RABIN

RICHARD I. WALKER

MILAN S. BLAKE

MICHAEL J. BRENNAN

NORMAN BAYLOR

FLORENCE HO

C O N T E N T S

P R O C E E D I N G S

(11:57 a.m.)

CHAIRMAN BORISH: This is Larry Borish and I would like to welcome everyone to the meeting of the Allergenic Products Advisory Committee, and I will start by introducing myself and I'll just say a couple of words to defend, explain why I'm sitting here in the chair seat.

I'm currently a professor at the University of Virginia in the Division of Allergy, and I'm actually on a sabbatical in Boston for six months. My interest in allergenic products goes back to a long line of research I've done in mechanisms of allergy and especially immunotherapy, which led to my being chair for many years of the Academy Immunotherapy Committee and the Biotherapeutics Committee, and I think my nomination for this committee came through the auspices of the Academy of Allergy, the College of Allergy.

And I immediately went from being a member of the committee to being chair without ever having attended a meeting. This is my first meeting, and you'll have to bear with me while I learn some of the ropes.

That is my defense of why I'm here. While

I don't have a specific research interest in allergenic products, I have a huge personal interest in mechanisms and what we're doing in this field, and the defense of this really comes down to a running joke. When I was the chair of the Immunotherapy Committee, given by innumerable Fellows, and the joke always went along the lines of, "What are you doing chairing the Immunotherapy Committee, Larry? You've never actually given an allergy shot in your life, have you?" which is something of an exaggeration.

Anyway, that is my interest and why I'm here, and let me turn the chair or turn the speaker over to Gayle for a moment, who will introduce herself and other members here today.

MS. DAPOLITO: Thank you, Dr. Borish.

I'm Gail Dapolito. I'm the Executive Secretary for the committee, and what I'd like to do is first check with the committee members who are on the teleconference. Can you hear us okay? If I don't hear a no, then I'll assume everyone can hear us okay.

I think we just had some members join us. Can I ask is Dr. Shepherd on the line?

DR. SHEPHERD: Yes, I'm here.

MS. DAPOLITO: Okay, and Dr. Wills-Karp?

DR. WILLS-KARP: Yes, I just joined.

MS. DAPOLITO: Oh, terrific. So what I would like to do now is I'll call the roll of the committee alphabetically, and if the committee members could introduce themselves please. Dr. Atkins.

DR. ATKINS: I'm Dan Atkins. I'm from National Jewish Medical Research Center. I'm the Director of Ambulatory Pediatrics here.

MS. DAPOLITO: Thank you, and Dr. Granady, I think, went off the phone for a few minutes.

Ms. Olson.

MS. OLSON: Hi. I'm a consumer representative. I'm a patient education specialist, and I work at the Mayo Clinic in Rochester, Minnesota.

MS. DAPOLITO: Thank you.

Dr. Ostrove.

DR. OSTROVE: Yes. I'm president of my own validation client's company. I'm a biochemist by degree and have worked in basic research and allergy research years ago while I was doing my doctorate and postdoctoral work.

MS. DAPOLITO: All right, and Dr. Portnoy.

DR. PORTNOY: Jay Portnoy. I'm the Chief of Allergy at Children's Mercy Hospital in Kansas City.

MS. DAPOLITO: Dr. Shepherd.

DR. SHEPHERD: Gillian Shepherd. I'm on the staff at Cornell University in New York, previously directing the clinical services in immunology, now in private practice.

MS. DAPOLITO: Thank you.

Dr. Wills-Karp.

DR. WILLS-KARP: I'm Marsha Wills-Karp. I'm Director of Immunobiology at Children's Hospital in Cincinnati.

MS. DAPOLITO: Thank you.

We have one speaker phone in our office, in our conference room here, and we have it on the highest volume. So I would ask the committee members to speak as loud as you're comfortable with for us so we can all hear you in the room.

Thank you.

And I'd like to go around the table and introDuce the FDA staff here. Shall we start with Dr. Slater?

DR. SLATER: Sure. I'm Jay Slater. I'm the Chief of the Laboratory of Immunobiochemistry in the Division of Bacterial, Parasitic, and Allergenic Products.

DR. RABIN: I'm Ron Rabin. I'm a Senior Staff Fellow in the Laboratory of Immunobiochemistry.

DR. BAYLOR: I'm Norman Baylor, the Director of the Office of Vaccines.

DR. HO: Florence Ho, Deputy Director, Office of Vaccines.

DR. BRENNAN: I'm Michael Brennan, the Associate Director of Research for the Office of Vaccines.

DR. BLAKE: I'm Milan Blake, Deputy Director of DBDAP.

DR. WALKER: I'm Dick Walker. I'm the Director of the Division of Bacterial, Parasitic, and Allergenic Products.

MS. DAPOLITO: Thank you.

I wanted to tell the committee on the phone we do have a few members of the public with us today, and other staff from FDA, and a video company FDAAdivsoryCommittees.com, just so you have a feel for what we are on site.

Dr. Borish, shall I read the conflict of interest statement?

CHAIRMAN BORISH: Yes, please.

MS. DAPOLITO: Okay. This is the conflict of interest disclosure statement for the Allergenic Products Advisory Committee Meeting September 13th, 2006.

The Food and Drug Administration convenes today's meeting of the Allergenic Products Advisory Committee via teleconference under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the committee are special government employees, and are subject to the federal conflict of interest laws and regulations.

Dr. Steven Ostrove serves as the industry representative acting on behalf of all related industry and is president of Ostrove Associates, Incorporated. Ostrove Associates provides consulting services to pharmaceutical clients in validation and regulatory affairs. Industry representatives are not special government employees and do not vote.

The following information on the status of this advisory committee's compliance with federal ethics and conflict of interest laws, including, but not limited to, 18 USC Section 201 and 21 USC Section 355(n)(4), is being provided to participants of today's meeting and to the public. FDA determined that members and consultants of this advisory committee are in compliance with federal ethics and conflict of interest laws, including, but not limited to, 18 USC Section 208 and 21 USC Section 355(n)(4).

Under 18 USC 208, applicable to all government agencies, and 21 USC 355, applicable to certain FDA committees, Congress authorized FDA to grant waivers to special government employees who had financial conflicts when it is determined that the agency's need for a particular individual=s services outweighs his or her potential financial conflict of interest, Section 208, and where participation is necessary to afford essential expertise, Section 355.

Related to Topic 1, the committee discussion of FDA's proposed strategy for reclassification of Category IIIA, allergenic products, members and consultants of the committee who are special government employees at today's meeting, including special government employees appointed as temporary voting members, were screened for potential financial conflict of interest of their own as well as those imputed to them, including those of their employer, spouse or minor child. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

In accordance with 18 USC Section 208(b)(3), the waiver was granted to Dr. Jay Portnoy.

A copy of the waiver statement may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

For Topic 2, the committee will receive an update on the research programs in the Laboratory of Immunobiochemistry, Office of Vaccines, Research and Review.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agency 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 relationships that you may have with any sponsor, products, direct competitors, and firms that could be affected by the discussions.

This conflict of interest statement is available for review at this meeting. Please see the Executive Secretary.

Thank you.

Dr. Borish.

CHAIRMAN BORISH: Thank you, Gail.

At this point maybe we should defer the next item on the agenda and move right on to Topic No. 1, which will be the proposed strategy for reclassification of Category IIIA, allergenic products, and I'll turn the meeting over to Jay Slater to handle this part of it.

DR. SLATER: Thank you very much, Dr. Borish.

First of all, let me just ask. We can hear the committee members pretty clearly. Can you all hear me very clearly?

PARTICIPANTS: Yes.

DR. SLATER: Okay. Terrific. Okay. Then we'll proceed.

And you should all have a copy of my presentation, "The Efficacy Review of Allergenic Products." Do you have that?

PARTICIPANTS: Yes.

DR. SLATER: Okay. Then what I'm going to do is as I go through these slides I'm going to identify the slide that we're on by number. The numbers actually appear in the lower right-hand corner of most, but not all, of the slides. So we may have some gaps, but I think it will be pretty clear.

First of all, I want to thank you all for participating in today's meeting and giving us your time to discuss these matters. What I'm going to talk about is a process that I actually talked about in our last meeting, which was held in April 2005.

Only some of you were actually in attendance at that meeting. We have new members and we have some members that were new at that meeting but couldn't attend, and so I'm going to spend the first half of this presentation reviewing some items that we discussed back then, and then I'm going to give you an update on where we have gone with this process.

Go to Slide 2, please.

So today's presentation will involve a discussion of prior efficacy reviews, and those are reviews that were done by two panels that were convened by the FDA. The first one was convened in 1974, the second one in 1982, and we'll discuss very briefly their work.

And then we'll bring the discussion up to the present and talk about our current effort at bringing this efficacy review process to completion. The process that was started in 1974 needs to be brought to completion at this time, and we'll discuss how those efforts have gone forward.

That's involved in initial screening of the remaining allergen extracts on the market, the construction of a database, the process of our review, including discussing some issues that our committee has encountered and how we dealt with them, and perhaps an idea of the time line for the completion of the process at this point.

Let's go to Slide 3.

This slide has a lot of information in it, but it's background that I think is of use. You're probably aware that the FDA operates under laws, and the first of those laws that was involved in allergen extract regulation was actually the Biologics Control Act of 1902.

The Biologics Control Act of 1902 was passed by Congress in the wake of a catastrophic event in St. Louis where 13 children died after having received a diphtheria antitoxin that was contaminated with tetanus spores.

The next significant act was the Food and Drugs Act of 1906, which was passed in the wake of disclosures about horrors in the meat packing industry as well as poisonous preservatives and dyes in food against the background flames of useless cure-alls as well and patent medicines that were dangerous. The

Food, Drug, and Cosmetics Act of 1938 was passed in the wake of the production of an elixir of sulfanilamide that contained diethylene glycol in which 107 people were killed.

In the wake of that, the efforts to regulate all biologic products as well as allergen extracts proceeded forward. Initially allergenics were managed by the hygienic laboratory of the Public Health Service in 1902. In 1930 the National Institute, not Institutes, of Health was founded and that took over the regulation of biological products.

In 1955, NIH founded a Division of Biologic Standards, which regulated biological products until 1972 when the FDA took over the regulation of these products.

At that time, the FDA convened a series of efficacy review panels, not just to review allergenic products, but to review all biological products.

Next slide, please, and this is a brief time line. You can skip now to slide number five.

What we are now going to talk about, however, are only the efficacy review panels that were convened to review allergenic products, but you should keep in mind that other efficacy review panels were convened for other biological products as well.

The purpose of the classification panels is indicated on this slide. The purpose is for reviewing biological products that have been licensed prior to July 1, 1972, that they are safe and effective and not misbranded. In the context of the initial allergenics reviewed, data were requested from manufacturers in two Federal Register notices, both of them in 1974. This panel did a significant amount of work working over a period of five years. They submitted their final report in 1981, which was published in the Federal Register in 1985.

Slide number six.

So, again, on our time line, remember that this 1974 to 1979 panel, which we're going to call Panel 1, reviewed all allergenic products, and what you can see on that designation for that panel, the panel categorized all allergenic products as one of four different categories, I, II, IIIA and IIIB, and we're going to talk about that in the next couple of slides.

Slide number seven.

The panel's task was to review all of the existing allergenic products. This is over 1,500 allergenic products at the time. Their goal was to evaluate the safety and efficacy of these products in

accordance with the regulations, to review the labeling of these products, to submit a report of conclusions and recommendations.

Slide eight.

These are the categories that were given to that panel. These are categories not that the panel actually set up for themselves, but that the regulations set up for them.

Those extracts that were put in Category I were extracts that the panel said were safe and effective and not misbranded. Any extract that the panel thought was either unsafe or ineffective or misbranded was placed in Category II.

Category III was for extracts for which the data were insufficient to place it in either Category I and II, and within Category III there were two subcategories. One was Category IIIA. Those were products that were thought in spite of their insufficient data to have a highly favorable risk to benefit ratio, and these were products that were left on the market pending completion of testing and evaluation.

In contrast, products that had an unfavorable risk-benefit ratio were Category IIIB, and these were to be removed from the market pending

completion of testing.

Slide number nine.

Let's talk about this in a little bit more detail. Category I products, those that were safe and effective and not misbranded could be so categorized based on what the panel called conclusive evidence, and for purposes of brevity here and because some of the panel members have heard this before I'm not going to go into this in great detail, but suffice it to say that conclusive evidence for the panel in 1974 is pretty much what I think you and I would consider to be conclusive evidence today. These were really controlled trials in a significant number of individuals that were scientifically well done and valid.

So conclusive evidence is a pretty high standard, and clearly, those products could be put in Category 1.

However, the panel also recognized that this was going to be a very small number of extracts for which conclusive evidence was available. They had a lower standard for allowing some items into Category 1, and that was acceptable evidence for which there was good scientific data but not necessarily well controlled or quite perfect in terms of its design.

Acceptable evidence could put a product into Category I if it was associated with widespread acceptance and use, clinical syndrome well documented, favorable in vitro changes, systematic observation for possible adverse events and for which the disease, the natural history was fairly well understood.

Let's go to slide number ten.

Products were placed in Category IIIA, that is, data insufficient for classification but may remain on the market for either acceptable evidence or circumstantial evidence, and slide number 11, products that go into Category IIIB, if there was insufficient evidence, and those products would be put in Category II if there really were no data whatever or if these was evidence of lack of safety or questions about risk-benefit ratio.

Slide 12.

So let's look at what the panel actually recommended with the 1,500-plus extracts that they looked at, and on this slide you see an important point, and that was that the panel recognized that they really didn't have 1,500 reviews to do. They really had 3,000 reviewed to do because each allergen extract had to be reviewed independently for its two important uses, and that was either to be used for the

diagnosis of allergic disease or to be used for the immunotherapy of allergic disease.

And you can see that the distribution of results were somewhat different. You can see here that very few products actually were put in Category II at all. The exception for this was foods for immunotherapy. All foods were categorically put in Category II for immunotherapy by Panel I, and because of that I actually don't include foods under the therapy column at all. I thought it would be more interesting to look at the percentages of the non-food products for therapy.

But very few products, only a small handful actually made it into category two for diagnosis.

What you can see here is that for diagnosis about 26 percent of the products they reviewed were put into Category I and 48 percent were put in Category IIIA, 26 percent in Category IIIB. For therapy only one percent were placed in Category I, 65 percent in IIIA, and 34 percent in IIIB.

Slide 13.

In addition to these broad recommendations, the panel made other recommendations for manufacturing principles, how to improve the

manufacturing of allergenic products, for studies that should be done on the IIIA products. In other words, the panel was very cognizant of the fact that putting products into Category IIIA was not a permanent approval, but rather a call for better studies to be done.

And in addition, the panel made a strong recommendation for ongoing allergen standardization.

Slide 13.

So the panel recommended for studies on IIIA products that these studies be done prospectively in FDA approved studies. They recognized that in order to do these well, they needed to be collaborative studies. They thought that it was important that there be separate studies for diagnosis and for therapy of these IIIA products.

The next point is an important one. The committee explicitly recognized that cross-reactivity was an important factor in allergenic extracts, and they certainly left the door open for inference among related allergens that allergens could be approved based on cross-reactivity data.

they also considered it to be acceptable in some cases for in vitro rather than clinical data to be used for placing products in Category I.

Slide 15.

In the report that Panel I issued that was published in 1985 was also included the FDA's responses to the panel's recommendations, and the most important response was that in spite of the fact that the first panel had initially been instructed to put products in Category I, II, IIIA or IIIB, shortly after this panel completed its work in 1979 to '80, FDA recommended that Category IIIA products should now be reclassified into Category I or II based on available data.

And, therefore, while this Panel I was actually in the process of writing up its report, Panel II was actually convened to do that.

So what you can see here on our time line is that the classification panel in 1974 to '79 completed its work and then shortly after that a reclassification panel was convened.

Now, in reality these panels had very significantly overlapping individuals, which I don't like here, but this was really a continuation of a very long job and very significant service for these people.

The reclassification panel was convened under another regulation and mandated that IIIA

products be reclassified as Category I or II. This panel met over a period of seven months in 1982 and 1983 and submitted its report at the end 1983. Slide 18 shows where this panel comes into play.

Slide 19.

So let's talk about what Panel II did. This is the reclassification panel. Basically all Category IIIA products were recommended for reclassification into Category I for diagnosis, except for certain extracts. In other words, most of the products were recommended for Category I, but some pollens, molds, mammalian inhalants were recommended for Category II.

And Panel II, and we'll talk about this a little bit more later stated that species definition was an important qualification for getting an extract into Category I. We'll talk about these nomenclature issues a little bit more later.

In terms of therapy, let's go to Slide No. 20. In terms of therapy, pollen extracts, animal extracts, and many mold and insect extracts were actually recommended for classification to Category I. Species definition was needed for reclassification to Category I, and many miscellaneous inhalant and all food extracts were recommended for reclassification

into Category II.

Slide 21.

So now we come to the task at hand, and the task at hand is to complete the process that was begun by Panels I and Panels II, and the way we have embarked on this is to review all of the recommendations for the Category IIIA products, review data that have been published since 1972, and then determine the FDA's position on the reclassification panel's recommendations based on the additional data that may have accrued over the past 20 years.

So if you go to Slide 22, you can see this time line, and you can see were we are relative to the process that has gone before us.

Slide 23.

So the current process involves first establishing a provisional process in which these Category IIIA products can be reclassified and to implement the reclassification. After that happens a proposed order will be published in the Federal Register that will include a listing of the FDA's reclassification of these products. It will include a period for public comment after the issuance of the proposed order, and at that point the FDA will

consider the public responses and revise the order as necessary.

After that happens, the final order will be published in the Federal Register, and the licenses or products that have been reclassified into Category II will at that point be revoked.

Slide 24.

So now we get into the real report on what we've done so far. The initial database contained over 1,500 extracts. Now, many of these were put in Category I or Category II by the original panels. We actually decided since there was some complexity of that, in other words, since there was some complexity of that. In other words, some products might have been a Category I for diagnosis, but Category IIIA for immunotherapy. In effect, the lion's share of these actually needed to be reviewed by us.

What we did not review and at the outset we decided we were not going to review, were any standardized products. There are 19 of those. We also decided that we needed to spend some time removing duplicate and obsolete entries. There were many of these products that even though they continued to be listed were actually not being manufactured and had not been manufactured for years.

So we spent a good amount of time looking for these obsolete entries. We also looked for duplicate entries and eventually pared it down to 1,273 entries, which more than half are pollens. The next largest group is foods, followed by molds, animals, insects, plant products, and dust.

Next slide, please. Slide 25.

At that point we realized we were going to have a large amount of data to manage, and we asked our IT department to help us to design a database that could be used for this purpose. We used a Microsoft Access based database, and it was important that we have provisions for good records for each extract that was reviewed, simultaneous access for all committee members of all records, a filing and organizational system of all the data that have been retrieved and saved, and the ability to generate final reports.

Although this was preliminary work, this was really critical preliminary work, and we had a great deal of help from, in particular, Richard Kapick and Nadja Davie in IT who really devoted and continued to devote a great deal of effort to keeping this database going.

Slide 26.

Because I'm just going to walk you through

some of these database panels to give you a sense of how we manage these extracts. What you see here on Slide 26 is the main panel that appears when you call up the database. The top drop-down menu is a searchable menu for the entire database of nearly 1,300 extracts. You can see that in this case we've selected a particular extract, cattle dander.

In the next panel below that says rationale, that is actually the final answer that the committee comes to after its deliberations. So I'm going to skip that. The next panel below is where the primary reviewer has indicated, but you should be aware that the way we've organized our meetings is that the primary reviewer does the review, but each extract is reviewed individually by all of the members of the committee as a group.

So even though there is a primary reviewer assigned to each extract, each extract is actually discussed at reasonable length by the entire group.

In the next panel below, we can designate by clicking the radio buttons what the previous two panels decided on each of the extracts, whether they were in Category I, II, IIA or IIIB. In some cases, we've actually found that the reviews have been absent even though we would have expected them to be there,

and so we have a "none" button as well.

Below that we can indicate which manufacturers make each of these products.

If you go to the next slide you'll see the bottom half of the main panel, and this is where the real core of our activity is focused.

The real center of the primary reviewer's activity is to search all available databases for information about these extracts, and therefore, it seemed important to us that we have a record of how these searches are actually conducted.

So under search strategy, the reviewer can record what strategies they used, what databases they searched. PubMed is obviously the major source of all of our reviews, but occasionally when there are no data in PubMed we search in ISI. In addition, we routinely search in non-medical, non-scientific databases or search engines such as Google.

In the comment section, this is really the narrative section. You really only see six lines of text here, but in the real database you can put as much as 150 lines of text, and this is the reviewer's opportunity to really go through in a narrative sense and indicate what his or her review showed.

In the panel below that is the folder in

which all of the data, usually PDF files, are stored and below that are the actual linkages to each of the PDF files or any other data files that are used.

If you think about it, if you do a search on a particular allergen, you may come up with articles or data that are relevant not only for that allergen but for other allergens. The database gives us the ability to link a single paper to multiple -- as many allergens as you want in the database, and I'll show you how that happens in the next slide.

So if you go to the next slide, this is the document data panel. So each of the documents that we use in our review are actually pulled up and the reviewer is expected to put in a fair amount of information about those documents, the articles that we pull up.

In particular, we can put in specific information about the vehicle that's used, what kind of immunotherapy. Design is described, extract concentrations, the study designs, if any, analyses, diagnosis, species used, statistical analyses and lot information. You see a small radio button in the upper right-hand corner. In this the reviewer can designate a piece of information as proprietary information. This is not a problem when the committee

is involved in its internal reviews, but certainly any proprietary information would have to be removed before any of this information were released to the public.

Below that you can see that the PubMed or ISI number is indicated. This is important for subsequent retrieval if any other problems occur with the database. Below that is a comment section where the reviewer can indicate in narrative form what the particular article has told them, and finally, below that is a way to link this particular source to any other extracts beyond the extract under review at the moment.

Next slide, please.

At this point we go back to the main panel. The reviewer has completed their individual review and at that point they need to make a decision as to the safety and efficacy of the product for both diagnosis and therapy so they click to update their rationale, go to the next slide, and this is the last one of these panels where the rationale panel is indicated.

Here the reviewer decides whether the product is safe and effective for diagnosis and therapy and indicates the reason for those decisions,

and you can see in the windows below the number of possible reasons, either clinical reports, cross-reactivity data, good peer reviewed article or in some cases authoritative text that form the basis of the decision.

So what have we done so far? This committee meets about every three to four weeks. We started out with a total of 1,273 entries. Seven hundred and forty-five individual reviews have been completed. Of those 745, the committee as a whole has reviewed 624. So you can see that on our track so far we are more than halfway done, which would seem not to be terrific progress sine we last talked about this nearly a year and a half ago, but in fact, the pace of reviews has picked up dramatically. Obviously as the committee gets more experienced, we're able to do things more efficiently, and I hope even better, and I think we are on target to really complete this process in a fairly short time at this point.

I'd like to spend the next few slides starting with Slide 32 taking you through some of the issues that we have addressed in the course of our review. Now, some of these have not been surprises. Many of them, in fact, were not surprises at all, but I really wanted to give the committee an idea of some

of the considerations that we internally have been dealing with in these reviews.

The first point I'd like to make is that our reviews continue to be generic and not specific. Generic is not a great word, but it's the word that Panel I used, and so I'm going to explain it to you in this context.

Panel I, the panel that met in the 1970s, recognized immediately that it had a significant problem. It had over 1,500 products, but it also had at the time 11 or 12 companies that were making the lion's share of these products. They had to decide whether they were going to review each company's product individually or whether they were going to review these products more generically.

And by generically, they meant that it relied on accumulated evidence and information about the substance itself. For the most part Panel I reviewed products generically. In other words, when they reviewed short ragweed allergenic extract, they reviewed short ragweed allergenic extract, not each individual company's short ragweed allergenic extract.

Now, in some cases, they did do some product specific reviews, and these are indicated on this slide, but they were very uncommon, and they were

certainly not the way that committee did most of its deliberations. Panel II continued in that vein, and we really saw no reason to diverge from that. We continued to do reviews in this manner.

Slide 33.

I indicated when I showed you the database that we could designate products, information sources as proprietary or private. I would like to report to you that the information that we reviewed so far has been entirely from public sources. We have received no proprietary information. We've received no information from individual manufacturers or from other nonpublished sources.

All of our data are data that are publicly available on the Internet, most of which, the lion's share, has been from Medline searches of English language literature. We have obtained some information from ISI, and very rarely from more general Internet searches.

Slide 34.

Product safety, and we talked about this at the last meeting in April 2005. The fact is that Panels I and II classified nearly all products as safe, with the exception of their reasonable recommendation that food allergens should not be used

for immunotherapy.

We have continued in that manner, and basically unless we have seen data suggesting that there were safety issues, we have inferred that the product is safe for diagnosis and even other than foods for immunotherapy.

A good part of our effort in our database searches is to look for safety problems. It's one of the main reasons that we do Google searches at all. It's really fairly unlikely that we're going to find efficacy information on a general database search, but actually following a suggestion from Dr. McDonald at the April 2005 meeting we have been doing a fairly aggressive searching for safety issues. That being said, when we have not seen safety issues in spite of our searching, we have concluded that products were safe.

Slide 35.

Likewise, following what Panel I and Panel II did, we have used in some cases limited data to provide information of efficacy on certain product. I'll give you some examples. For grasses, trees, and weed pollens and for animal extracts, there's a significant amount of data that as a group these products are efficacious and safe for immunotherapy.

Therefore, when we have found evidence that products are efficacious for diagnosis among these groups, we have placed them in Category I for therapy as well.

Another example of using limited data for efficacy on certain products is that in general, as we discussed in our April 2005 meeting, we have required that we have two or three case reports to support the efficacy of products.

In the case of foods, we have in some cases considered a single case report supportive of skin test diagnosis if that same case report has supportive oral challenge data as well, and likewise for other allergens we have in some cases accepted single case reports for skin test diagnosis if the same case report included supportive challenge data, either nasal or bronchial or congentival challenge data.

So these are examples of where, if you will, we have sort of leveraged some data to support efficacy for other products as well.

Slide 36.

One of the problems that we encountered early on was how to handle food studies in which the actual studies were done with the foods themselves

rather than with extracts. This is not particularly a problem for other extracts.

In other words, the committee has not really been getting into the details of how extracts are prepared for the most part. We know that when somebody makes a pollen extract and does a study, it's going to be pretty much what the commercial manufacturers are using, and we can infer from those data to what the manufacturer might be doing.

The underlying assumption is that most allergens are water soluble and stable when properly stored, but it's clear that that assumption is not valid for food allergens, and therefore, we decided fairly early on that data will be considered supportive of the efficacy of food allergens for diagnosis only if the extract was prepared by a method comparable to those for commercial methods.

Therefore, data using fresh or unfiltered pulp or juice or slurries even if they're relatively convincing are not being used to support the efficacy of an allergen extract for the food allergens.

Slide 37.

Following the recommendations put forth in both Panels I and Panels II, products may be placed in Category I based on cross-reactivity. If an extract

is shown using either in vitro or in vivo data to be cross-reactive to another extract for which good efficacy data exists, the other cross-reactive extract may be considered to be effective as well. Partial cross-reactivity, which is really the rule, not the exception, is acceptable.

When quantitative cross-reactivity data are provided, the degree of cross-reactivity should certainly be no less than 20 percent for allergens of the same genus, and for allergens of different genera, the minimal level of cross-reactivity should be higher.

This is an important point, the last one on Slide 37.

When cross-reactivity between two or more extracts of the same genus are especially convincing, and that's true for a number of genera, then additional members of the same genus may be determined to be cross-reactive as well.

And this has come up in a number of allergens, especially some tree and weed pollens, where there may be very convincing data on efficacy for one or two members of a genus, some good data that suggested that there's extensive cross-reactivity among those members of the genus. Therefore, we have

in some cases inferred efficacy for other members of the same genus.

Slide 38.

And this point is actually covered in both Slides 38 and 39, and this was, I think, a bit of a surprise to us. Let's talk about the specificity of source material nomenclature. Panel I, and it's a report that I would recommend that you read -- it's actually very interesting reading from the 1970s -- it turns out Panel I made a big point of saying that specific designations and names for the source materials had to be given, but they did not really require that it be genus, species scientific nomenclature.

They were concerned simply that the name be highly specific, short ragweed pollen, for instance.

When Panel II came around, they actually introduced the idea that genus and species names should be required for pollens, molds, and plant extracts.

And slide 39.

When we started our deliberation, it seemed to us that it was intuitively clear that we would insist on genus and species nomenclature for all

of our allergen extracts. We quickly realized that that was a little bit naive. We found several cases in which genus, species naming was confusing and several cases in which they were not helpful.

For instance, and the examples that I give are almost entirely in foods, and that's because with the other extracts, there really are extensive scientific databases to help us negotiate this, but with foods it's somewhat more difficult.

For instance, multiple different beans, navy beans, pinto, red kidney, green beans and yellow wax beans, all share the same genus species names. There seem to be different strains of the same species.

If you look in databases to look at the name of flounders, you find three genera that are designated, but no specific species oddly enough. And in fact, if you look at many of the articles, most of the articles about flounder allergy, they don't designate any genus or species at all. They just say flounder.

And likewise catfish articles, we were unable to find any articles that designated genus and species at all which wouldn't be a problem, except that there are several different species that are

called catfish.

Lobster it turns out is even more complicated. There are 36 different species of lobster that are reported in the FDA's own database, but the articles never indicate the genus and species. Now, again, you can deal with some of these issues, but they require some flexibility and some inference.

For instance, we can probably infer that many of these investigators simply go down to the local grocery store to buy the products that they're testing with. If they happen to be in Maine, you know that it's probably Homarus americanus, but you can't really be sure, and it's hard to interpret these things.

So we have had to confront some of these issues, and we actually haven't quite resolved them yet. This is an ongoing problem. We are in the midst of consulting with experts both in nomenclature and in food allergy, but this is going to be an ongoing issue that we haven't resolved yet, and we are going to have to try to resolve before we issue our final reports.

Needless to say, Slide 40, we have learned a great deal about nomenclature, species naming, species synonymy, and with the exception of foods, we've actually learned quite a bit that has helped us.

There are terrific online databases. NCBI's taxonomy database is really terrific. The National Museum of Natural History has a wonderful database devoted specifically to mammals as well as to seafood. There are, believe it or not, USDA has outstanding plant databases that have really helped us quite a bit with our pollen extracts.

And for seafood, in spite of the fact that the information is often contradictory, there's a huge amount of information both from FDA based databases, from independent databases such as fish base, and from the Museum of Natural History.

And for the molds, there's a database that I promise you I never knew existed before called Index Fungoram that has been extremely helpful and actually has helped us resolve many, many issues with the mold extract.

So Slide 41.

This is my report to you on our progress so far in the completion of the 601.26 process. We are about halfway done, but my guess is that in terms of timing we are probably three quarters done in terms of our time line.

I hope to have this process completed over the next five to six months, and we certainly are

aiming for that. The committee members are very energetic.

By the way, it was asked at the last meeting how many people were going to be involved in this. It's ten. So it's a lot of work. Very hard working people who have a lot of other things to do in terms of their jobs here at FDA, but we've had really good reviews by everybody, good discussions in the committee as well.

Fortunately we've not identified any broad safety issues, and you can imagine having reviewed over 700 products with ten individual reviewers really aggressively looking for safety issues it has been reassuring that we have not found them.

And then finally just to point out that our evaluations are just about exclusively based on really -- I won't qualify that -- exclusively based on published data, readily available data in the databases.

CHAIRMAN BORISH: Well, thank you very much, Dr. Slater, for that great report.

Actually, before we continue, is Dr. Granady back with us?

(No response.)

CHAIRMAN BORISH: I'll take that as a no.

I think before we open this up to a general discussion I'd like to begin maybe with just specific questions on Dr. Slater's presentation that people may have. I know I have a couple. Does anyone want -- hello?

MS. DAPOLITO: Dr. Granady, are you with us? Well, it must also have a sign-off.

CHAIRMAN BORISH: Okay. I have two questions for Dr. Slater. Does anyone else have any specific questions they want to ask him just right for now about his presentation?

(No response.)

CHAIRMAN BORISH: Okay. I'll ask my two.

The first one is I may have missed this, but what is the status of IIIB? That seemed to disappear after the mid-'70s report. Are there still products in that category? And what are we doing with them?

DR. SLATER: No. The IIIB products were designated to be removed at that time. There were not many IIIB products, but the Category II and the Category IIIB products were designated to be removed, and we have not come across those in our review. So they are gone.

CHAIRMAN BORISH: And the Slide 35 --

DR. SLATER: I'm sorry, Larry. Hold on one second.

MS. BRIDGEWATER: I'm sorry. I just want to say the final order request by the category IIIB products was published in 1994, and that is in the Federal Register.

I'm sorry. This is Jennifer Bridgewater from FDA.

CHAIRMAN BORISH: So that was the final order reclassifying them as Category II?

MS. BRIDGEWATER: Yes.

CHAIRMAN BORISH: Okay. Now, in Slide 35 you say for grass, tree, weed and animals, the preponderance of evidence of safety. That leaves off one very large category, and I'm sort of curious how the previous committees and your group has dealt with the issue of mold, especially mold in terms of therapeutic because although you could find an occasional study suggesting some efficacy, any kind of retrospective analysis would say the preponderance of data is that these agents are, in fact, not effective as therapeutic.

I'm just curious how you dealt with that issue.

DR. SLATER: Well, that's a good question.

You're quite right. Let me say the positive thing first. Again, there's a fairly rich literature having to do with these various pollens and animal extracts, that these are products that if you're allergic to them and you can be given them safely, they can reduce your allergic response. In other words, allergen immunotherapy can be effective for them.

The data on molds are controversial and are, you know, hard to interpret. Therefore, when we've been reviewing mold extracts, we have not inferred efficacy for immunotherapy even if there were good data to support efficacy for diagnosis.

So that's the difference. In other words, for the mold extracts, in order to support a Category I designation for therapy, we actually had to have some data that suggested that the extract was effective for therapy, and we didn't just infer it on the basis of the fact that there are allergic diseases and you can skin test people for the extract.

CHAIRMAN BORISH: So by and large, it sounds like most of the agents currently available are going to be moved into this Category I for diagnosis and therapy. The exception may be mold. It may be approved for diagnosis, but not therapy.

Now, are there implications of that?

DR. SLATER: Okay. So let's be perfectly clear. We're not commenting on how many of the products are being -- we haven't completed the process yet. So we don't know.

CHAIRMAN BORISH: Understood.

DR. SLATER: All we're saying is that if a pollen extract or an animal extract has been shown on the basis of data or cross-reactivity data to be shown to be effective for diagnosis, then we are putting it into Category I for therapy as well.

If a mold extract is shown to be effective on the basis of data or cross-reactivity data, to be effective for diagnosis, we are not necessarily putting it into Category I for therapy.

That doesn't mean that it won't be ultimately on the market. It simply will go into that same group as all of the food extracts that will say, you know, for use in diagnosis only.

But you're quite right. The mold extracts were not included in that group, and that's intentional.

CHAIRMAN BORISH: Another specific questions regarding Dr. Slater's presentation?

DR. WILLS-KARP: Eric, can I ask one question? Is there any concern that adverse events or

negative data may not have been published?

MS. DAPOLITO: Is this Dr. Wills-Karp?

DR. WILLS-KARP: Dr. Wills-Karp.

MS. DAPOLITO: Thank you.

DR. SLATER: It's a good question. I think that whenever you talk about adverse events you certainly have to worry about how sensitive your system is to detect adverse events. That being said, when you look at reports, and there certainly are many articles about adverse events during allergen immunotherapy, they have not really focused on particular products. They have really focused on particular patient profiles, and particular regimens of immunotherapy: rush versus conventional. They have focused on medication errors in terms of dosing.

They have not really focused on individual products or even classes of products so much. Certainly our ability to collect safety data is only as good as the reporting of this information, and I certainly will acknowledge that it's possible that we're going to miss some safety reports even if we're trying very hard.

It's one of the reasons that we really discussed this in April of 2005, are discussing it today. This process is still ongoing. Certainly we

are open to receiving nonpublished information about practice, but we have not received that yet.

CHAIRMAN BORISH: This is Dr. Borish.

I just want to suggest that when people talk they introduce themselves first so we can know who you are.

One of the interesting points, what Dr. Wills-Karp just said, is presumably foods are falling from what you just said, foods are falling into the category of not being safe for treatment largely because they are so risky for treatment because of the issue of anaphylaxis and death.

So there we're using anaphylaxis and death as a category not to prove it, but clearly a lot of the safety issue with all of the extracts is that deaths have occurred with all of them, but in the case of non-food allergy, we're accepting, well, near death and death as an acceptable risk, I guess, is the thinking.

You're looking for safety. So you understand what I'm asking. Safety is non-issue for an inhalant allergy, yet it becomes an issue for food allergy.

DR. SLATER: No, it's clear that there's a risk for allergen immunotherapy not matter what the

allergen that's used. We understand that, and the practitioners understand it and hopefully the patients who undergo allergen immunotherapy understand it. That risk is actually quite small.

The reason that Panel I and Panel II put all foods into Category II for immunotherapy is that there seems to be some widespread consensus, some of it based on experience, that treating food-allergic individuals by immunotherapy was unusually risky; that even though there may be benefits associated with it, the risk was unacceptably high.

And, therefore, it's not just the end point and the types of adverse events. I think it has to do with the frequency of the adverse events and the frequency of the risk.

So, you know, I have to say the current group at FDA certainly agrees with the Panel I and Panel II's conclusions regarding food allergen immunotherapy at this point.

CHAIRMAN BORISH: Before we continue, I just want to make a general comment or two general comments. I mean one is that this is clearly an essential activity of the FDA. You know, as a consumer I find it, frankly, for lack of a better word, unacceptable that we have thousands of products

sitting on the market that have never had any kind of a supervision and are sitting in this no man's land of never having received any kind of an approval process.

But, you know, it should be very clear to all of us that there are huge implications to the decisions we're going to make today. There are a lot of practitioners -- I don't think a majority, but certainly a large minority -- whose practices are going to be severely impacted by the decisions to move a lot of their extracts into Category II.

There are also some manufacturers for whom this is going to have a huge impact. I think there are manufacturers out there who have sort of made a career, have found a niche of providing or addressing products that have been dropped, if you will, by some of the larger manufacturers because of the perceived concern over the value that they provide for the allergen community at large.

So we need to have a serious discussion as to what we're doing here today and be very comfortable that we're going to remove a large number of products from the market potentially.

DR. SHEPHERD: Larry, Gillian Shepherd. Can I interject a question?

CHAIRMAN BORISH: Please.

DR. SHEPHERD: Jay, I know you've been focused on published data. Are you also including MedWatch in your review for possible adverse reactions?

DR. SLATER: Gillian, do you think that adverse reactions to allergens reported to MedWatch very much? We initially stated out saying that we were going to do that. It turns out it's not a very common mechanism for reporting, and very often what we're getting more is noise than actual information.

Do you have a different sense of the value of it at this point?

DR. SHEPHERD: No, my only bias is that a lot of busy physicians might send a report into MedWatch, but would not take the time, as Marsha was concerned, to actually make a published report.

DR. SLATER: We can certainly do that.

DR. SHEPHERD: it probably wouldn't take very much time to just scan and make sure that you're not missing a specific adverse reaction.

DR. SLATER: No, I think that's a good idea.

DR. SHEPHERD: My second question is to Larry or to Jay because I'm a new member of the committee. Could you just define for me exactly the

role of this committee on the phone today with regard to this process?

Jay you said that there are ten FDA members that are doing this review. Specifically what is the responsibility our committee?

DR. SLATER: Yes, I'm sorry. I didn't really make that clear.

The purpose of this presentation is really to report to you on what we are doing. It's really information only. We're not asking any specific questions, but I really would fully welcome any comments and suggestions that you have about the process. You know, I appreciate the MedWatch recommendation and any other ones that you have.

We view this as the completion of really a very public process that was started in the 1970s and 1980s. At this point, as we said in our April 2005 meeting, we are not asking for outside experts to come in and to help us at this point. We are comfortable that we can complete this with our internal staff.

And in the end, we are going to report to you on what our decisions are, but that will also be by way of reporting.

The committee today, I think, is serving to help us with this process by giving us any comments

or advice about the process as I've described it to you so far, but I'm not asking you to make any decisions about it at this point.

CHAIRMAN BORISH: Well, a specific question since I'm also new in this committee and since clearly we are an advisory committee and we'll do that function. But at the end of this process for the next hour or so are we going to go on record officially with a vote, if you will, saying that we are giving our consent to the approach you have taken?

DR. SLATER: No.

CHAIRMAN BORISH: No.

DR. SLATER: This is a process that was started. We've reported on it last time. We're reporting on it now. It's a process that we have to finish. We have no real choice at this point.

CHAIRMAN BORISH: So this process is going to go ahead, and it's going to go ahead with a record that an independent advisory committee at least had an opportunity to give you.

DR. SLATER: To comment.

CHAIRMAN BORISH: To comment upon it. so perhaps to go back to my point about what the implications of this might be, it might help some of the other committee members if we give some focused

example of what kinds of extracts are potentially not going to be available to practitioners in a year or so.

From my listening to your report, an obvious example would be something like dust where you're handed a bottle and absolutely no information whatsoever as to what might be inside that bottle, one, a dozen, hundreds of different products many of which may or may not be actual allergens. Presumably there are other mixes like that that would clearly be unacceptable, but maybe if you could just give some specific examples.

DR. SLATER: Actually specific examples is probably something I can't give you. In the case of dust I can tell you right now we haven't reviewed it yet. We're saving that for later on.

I think that --

CHAIRMAN BORISH: Well, categories.

DR. SLATER: Poorly characterized allergies in terms of species designations. We have in our deliberations so far, although certainly that could change, we have been reluctant to putting Category I mixes or extracts in which only the genus was indicated, but it could be any species from that genus.

CHAIRMAN BORISH: You've been reluctant to?

DR. SLATER: To put them in Category I.

CHAIRMAN BORISH: Okay.

DR. SLATER: Unless there was some specific designation.

CHAIRMAN BORISH: There have been some extracts, a fair number of extracts that there has been quite a bit of ambiguity as to what the source material is from me, from what information we have, and in those cases we've been very reluctant to put them in Category I. We have put them in Category II.

DR. GRANADY. This is Lynelle Granady.

CHAIRMAN BORISH: Hi.

DR. GRANADY: You gave us a very extensive list of Category I, Category II extracts at the last advisory committee meeting. Maybe it would be helpful to provide that for the new members.

DR. SLATER: Are you talking about the first panel's report?

DR. GRANADY: Right.

DR. SLATER: I think that's a good idea. I think we can certainly send out a PDF file.

DR. GRANADY: -- a sense of what you're referring to.

DR. SLATER: Right, right. I think that's not a bad idea. Thank you.

DR. ATKINS: This is Dan Atkins.

I have another question about have you looked at the use of the different products. I mean, because that might have implications as to what your decision -- you know, how that impacts other people. At this point whether you use it or not, have you looked at that? Have you looked at these extra?

DR. SLATER: You mean whether the product is used at all?

DR. ATKINS: Right, whether it's used at all or whether it's, you know, widely used.

DR. SLATER: You know, the fact is Dan, we really don't have any good way of learning that. I think that's hard for us to really assess in an objective way, and certainly, you know, we could sit around the room and try to decide whether something is used, but many of these products are regional, and so it's really hard for us to assess that.

In a sense we're trying to get around that by allowing for cross-reactivity information to be used, but it is hard to assess that. Was there a particular example that you had in mind?

DR. ATKINS: Well, no, I am just concerned

that there may be an extract. Somebody is on an allergen extract that they're getting immunotherapy for and now we decide that there's not enough evidence, but it's widely used. Now you pull that out of everybody's extract and people are worrying, you know, that you changed their extract and why.

DR. GRANADY: I think you'll be more comfortable when you see the list though.

DR. ATKINS: Okay.

VIDEO OPERATOR: Dr. Granady, if at all possible, could you speak a little louder?

DR. GRANADY: Oh, I said that I think that you will feel more comfortable when you see the previous report because many of those allergens are allergens that we do not use, and that we don't have available routinely anyway. I don't think there was as much discussion about it, with it, you know, while we were able to see it.

DR. SHEPHERD: Hi. Gillian Shepherd.

CHAIRMAN BORISH: Hi.

DR. SHEPHERD: Another question. You're going to come out with a report that says that these various extracts, particularly plant extracts, are Category I for treatment, but there's obviously a lot of data that mixing these extracts affects their

efficacy. Are you under the umbrella of the FDA going to add any comments or recommendations about their use for treatment whether they be mixed or not?

DR. SLATER: It was not our intention to do that. Panel I actually had an extensive discussion about mixing. Of course, that was current as of the 1970s. It was not our intention to include anything that had to do with that.

Remember we're going to be issuing a proposed order, and that order certainly wouldn't have any comment about mixing. Are you suggesting that we should?

DR. SHEPHERD: Well, I think that most people are aware of that through currently published data, but I think the it would obviously -- it strikes me initially that that is something appropriate for FDA because if you're mixing these incorrectly, you're not getting the proper therapeutic effect.

From a safety point of view it's somewhat moot because you're decreasing the relative concentrations presumably.

DR. SLATER: You know, I think the problem with that, we can certainly consider it. I think the problem is that it was not our intention to not only review all the extracts for safety and efficacy for

diagnosis of the therapy. It was certainly not our intention to get into issues of dosing and treatment regimens and things like that.

I think that would probably go into the category of dosing and treatment regimens. I think what you're raising is a very valid point. It is certainly a concern, but probably doing that kind of a review and rendering that kind of a decision on a body of extracts that perhaps will number in the many hundreds would be very hard to do in a scientifically defensible manner.

That's my opinion, but I think we'll certainly talk about it as a committee.

CHAIRMAN BORISH: You're setting the bar very low, which is, I guess, a good thing in many categories, and one of them, of course, is equating efficacy with B in therapy with the diagnosis.

For diagnosis, of course, the dose response curve is amazingly flat, as Dr. Nelson among others have published. You have to make an awful lot of Serial 10 dilutions before you see a skin test disappear, whereas the window for -- let me go back.

At the high end at least for prick testing you may not be able to get enough allergen in solution to endanger a PRIC test, whereas clearly the

therapeutic window for therapy is very narrow, and the preponderance of data is we need to get a quite high concentration.

So, for example, you could imagine a scenario where there are diagnostic extracts for a cat that are clearly perfectly good for diagnosis, yet proven ineffective because the concentration of Thelzine 1 is so negligible, but you're comfortable with that at least aspect, that there are a lot of extracts that really are good for skin testing, but probably aren't for IT.

DR. SLATER: Well, I think you raise a good point. Again, I guess this goes back to Dr. Shepherd's point. I guess we were not plunging into issues of dosing and dosage regimens. Frankly, because, again, we're dealing with hundreds and hundreds of extracts, the complexity would really be too great if you concluded that one particular genus and species was effective for immunotherapy based on data. Would you then have to go through dose-response considerations in terms of the cross-reactivity in order to draw conclusions, the level of complexity would be fairly high.

And it's not so much that I'm unwilling to tackle that level of complexity. I'm just not sure

when you try to confront that if what you come out with at the end would be at all valid either in deciding yes or no for specific extracts.

What I want to get away from is having these IIIA decisions be random in any way or simply based on noise rather than real information. So it would be, I think, hard given the literature on allergen extracts, and especially the literature on allergen immunotherapy, which is really focused on a very small community of allergens. It would be really hard to raise too many fine points in terms of each individual allergen.

It does seem to me though that we could make a reasonable decision to say that, no, they're just going to be Category II for immunotherapy unless there's affirmative data. We've decided not to do that, but I hear your point, and I hear this part of the discussion. We certainly can reconsider that approach.

CHAIRMAN BORISH: I'm leading you, by the way, and I guess one question, of course, is, as I said, the bar is being set very low, but presumably we are giving ourselves the option of some future meeting or decade to readdress the then Category I extracts and say this was a fine standard for 2006, but maybe

in 2010 or '12 maybe you'll want to come back and say we can do better than this and then, I guess, reopen that and come up with maybe a better system of judging safety and efficacy.

DR. SLATER: I think that that's not going to happen. I think that -- and I'm staring at the industry representative sitting over there --

DR. OSTROVE: May I ask a question here on this. Steve Ostrove.

From the industry side, it looks like Slide 37, you indicate that you have a 20 percent cross-over in the same genus, and for different genera you expect to have a higher -- it would be a lower cross-reactivity.

Would you be setting standards of that nature for manufacturers for production issues?

DR. SLATER: No.

DR. OSTROVE: So standards would be set that they would have to meet at this point or at that point, I should say?

DR. SLATER: No. This is not -- this is not an effort to set new standards for the manufacturer. This is an effort to work with the data that we have to try to make decisions about existing extracts.

DR. OSTROVE: Okay.

DR. SLATER: That were present before July 1972.

CHAIRMAN BORISH: See, the problem with not opening this up in the future is that you eliminate any incentive to come up with improved standardized extracts. If we are going to have for all time a cockroach extract with no cockroach or with minimal cockroach allergen in it, what is the incentive for industry to come out with a standardized Logene 1 extract?

DR. SLATER: So this process is independent of standardization which proceeds on its own track. Regardless of whether a product becomes Category I based on this process, in other words, there's a preexistent nonstandardized product or a nonstandardized product that has been approved since 1972. The process of standardization is that when the FDA decides that the data and the technology are available to standardize an extract, it proceeds with standardization of that extract.

So I think you're bringing up cockroach is a very good example. We are in the midst of the process of standardizing a German cockroach allergen extract. We've done some studies, and we're going to

proceed with more, and my hope is that within the next few years this will actually happen.

It doesn't really particularly matter that cockroach be put in Category I at this point, but certainly the data are accumulating that suggest that it will.

But even if it is put in Category I, the manufacturers will have to comply with standardization when that happens on a separate scale. I think it's important to stress that this is an effort to complete this efficacy review. Efficacy review was never construed as an open ended, ongoing process. Certainly any product about which new compelling data arise that suggest that it's not really safe or effective, that can be reviewed by FDA and action can be taken.

But this is a process that once we complete it, will, in fact, be complete.

CHAIRMAN BORISH: Okay. Other comments?

DR. ATKINS: Dan Atkins.

this is certainly a tremendous amount of work. I appreciate the fact that your committee has done this. Is this database going to be open to the public?

DR. SLATER: I can't answer that yet, Dan.

DR. ATKINS: Okay.

DR. SLATER: I don't know. I can tell you that thus far nothing proprietary has occurred. Really, quite honestly, all of our deliberations have been totally generic. The committee's deliberations, nothing proprietary has occurred. We simply haven't decided from a technical point of view whether this is all going to be released to the public. You raise a good question.

DR. ATKINS: I think even for the physicians describing this extract it would be great to have this information available.

DR. SLATER: In what sense? I'm sorry. Do you want to -- I'd like to know what information you'd like to have available.

DR. ATKINS: So that they could go to an extract, look it up, look at the data about efficacy. You know, you've got all of the articles listed. I mean, there's a lot of information there. You have your summary.

DR. SLATER: Dan, to be honest, it's the first time I ever or anyone ever raised the idea that practicing physicians would find this database useful. I think that's very --

(Laughter.)

DR. SLATER: No, no. That's important. I appreciate it, and we'll have to give that some thought. I think you're raising a very good point.

CHAIRMAN BORISH: You found every published article on that extract, and you have the PDFs. It's a priceless data source.

DR. SLATER: Actually the PDFs can't be made available. No, that I can tell you right now. We can make the references available, but the PDF -- you all understand this -- are obtained, you know, through our license with Medline. One of the reasons that if you remember I was asking for the PubMed numbers is that if we did make this public I would actually issue a bibliography so anybody else could access the articles, but the PDF files themselves would actually have to be redacted out.

DR. RABIN: This is Dr. Rabin.

I would also just clarify that we don't necessarily have every reference. I mean, if there are certain allergens where, you know, there are 20 papers that prove the point that the allergen should be placed in Category I, most of us will stop at two or three.

CHAIRMAN BORISH: And most of us don't need help finding the studies that had allergy works.

DR. RABIN: Right.

CHAIRMAN BORISH: It's the obscure ones.

Now, some of this -- I just want to be clear of the approval process -- could be based on I guess for lack of a better word sort of a subjective impression. Somebody publishes their experience with this extra act and they have a few positive tests, and they think it's useful diagnostically.

It occurs to me that it might be useful for there to be some documentation somewhere that an approved extract actually has an allergen in it, meaning that there is some protein in there to which somebody somewhere once made IGE to. Is that something we could ask for?

DR. SLATER: No. Well, yes.

CHAIRMAN BORISH: Well, we could ask.

DR. SLATER: I can tell you right now that our approach has been to look for evidence that there is an allergic disease associated with the allergen, and that extracts prepared from this allergen can be used to diagnose or treat that allergic disease.

In the case of the first qualification, we certainly looked at specific IGE data. For many allergens there is specific IGE data that suggest that

that allergen actually elicits an allergic response in a certain subpopulation of humans, and we've looked for information that suggests that this disease can be diagnosed or treated.

In terms of saying that the extract bottle actually contains an allergen, that's actually a product specific review, and that's something we really -- it's hard to access that information without trying to access manufacturer specific and product specific data because one manufacturer may have a lot of allergen in it the other may not. So that's a little hard to do.

CHAIRMAN BORISH: But if you have a problem, you know, fall allergies, there's a specific disease. And I decide that fall allergies is caused by goldenrod, and I can now do a study where I say here's seven people who I used a goldenrod extract and found it to be diagnostic of fall allergies.

DR. SLATER: Right. The data aren't all equally strong.

CHAIRMAN BORISH: But you are prepared to move goldenrod -- I know we don't want to be specific, but flowers. How about as a flower pollen into Category I based on the current literature?

DR. SLATER: Well, you know, we have to go

somewhere, and obviously if we had our druthers we would need good, well designed trials to demonstrate allergenicity. It would be hard to find those, and I might add it would be hard to find those in spite of the fact that in 1985 this was specifically requested by the first review panel and reiterated by a subsequent panel since then.

It's clear that for a large percentage of allergen extracts this kind of data are simply not available, and, you know, I think that the decision that we've made as to what kind of data to entertain to decide that something is efficacious I think is a reasonable decision, but it's certainly not an airtight decision, and we all recognize that.

CHAIRMAN BORISH: But just to reiterate, you're setting a bar, and I'm obviously playing devil's advocate, and clearly any standard that I would like to propose would cause a furor in the industry and allergy community that was based on any kind of scientific merit. I'm just curious in my own mind since you're not going to answer the questions. What possible extract doesn't meet these criteria?

And I guess it's just coming down to somebody had better figure out what kind of Homarus they're treating, Homarus being the genus of lobster

for those who missed that part of Dr. Slater's talk.

Okay.

DR. SLATER: I think, you know, you raise some good questions, you know, and I can tell you right now that as a group we sort of grapple with these at every -- you know, where, what kind of data, what kind of evidence are really strong enough?

You've said repeatedly that we're setting the bar low. I agree that we're not setting the bar high, but there are many extracts that are not meeting these qualifications. So --

CHAIRMAN BORISH: And you're setting it low and refusing to consider coming back at a later day.

DR. SLATER: Well, coming back at a later day from a reasonable point of view really should not happen. I mean, this is, you know, a process in which we're being asked to decide which ones are efficacious, and this is a process that will end at this point.

But standardization will not end, and the improvement of allergen extracts will not end as well. They can still be --

(Pause in proceedings for audio interruption.)

CHAIRMAN BORISH: Clearly there must be some frustration from people sitting around this table, that for 30 years you have been demanding these data, not receiving the data, and now the people who should have created the data and didn't provide the data are basically being rewarded with approval of their process with their products.

MS. DAPOLITO: Could we ask if possible for the committee members to mute when they're not talking? Thanks.

CHAIRMAN BORISH: I may be nearing the B I'm at the end of my discussion. I don't know. Do any of the other committee members have comments before we open this up?

DR. SHEPHERD: It's Gillian Shepherd. Just one. I unfortunately echo everything that Larry said. I t is a bit frustrating.

Jay, you're saying that, for example, cockroach is efficacious based on your criteria. Are you comfortable that the standardization process then is such that the cockroach manufactured by the different companies does meet this efficacious criteria? There's enough protein in it or for any one of the extracts? You're saying globally it's effective.

DR. SLATER: Right. I mean, again, this is setting the -- these are the principles that were really established by Panel I, that they were going to review, if you will, an extract generically, and I'm going to stay away from specific extracts. I apologize, but I really don't want to discuss specific extracts.

But if the committee decides, if our group decides that there are enough data about Substance X that when properly extracted it can be used to diagnose and/or treat a legitimate allergic disease, we are not going into each individual manufacturer's methods for making it.

Certainly if there were any data that we found that suggested that no manufacturer could make an Extract X in an effective way, then we would take that into consideration.

But we're not going into each manufacturer's individual method. Is that a weakness in this approach? It certainly is, but it's a choice.

I think if we chose to review each manufacturer's data, it would actually be much less likely that we could apply some of the scientific papers that we have to any individual manufacturer's product because then we would have to link the

specific methods that were used in that specific academic paper to each individual manufacturer's product, and that would be, frankly, impossible to do in the vast majority of cases.

DR. OSTROVE: If I could once again step in, this is Steve Ostrove.

From a manufacturer's perspective, I think just guidelines as to what would be expected or the concentrations necessary to meet the requirements is the kind of information that we would be looking for and want to have, that I would need to go to one of my clients in order to work with them.

The specific manufacturing process may or may not be the key here, and that would have to be process validated at the end anyway. So I think that's just a guideline as to the levels or the minimum standards whether it's coming out of this committee or your data here that you're generating. I'm not sure, but I think it would have to be set in order to do something along the lines that's being talked about.

DR. SLATER: Dr. Ostrove, that's not part of this process, and I think it's important to clarify this. The end of this process is not going to be a situation in which we're citing to the manufacturers

anything about their methods at this point.

DR. OSTROVE: Not necessarily about the methods, but that's what I was wondering about the standardization before the limits that you were going to be setting, if any, as to whether that would be coming out of this.

And I understood or at least I think I understood that the numbers or levels would not be set from this and just looking to see from the data that's out there right now as to whether you consider it safe or efficacious or not.

DR. SLATER: That is correct.

DR. OSTROVE: Okay. Okay, fine. Thank you.

CHAIRMAN BORISH: Well, with Gillian's support I'm getting more frustrated, and I'm going to be more vocal. I'm bothered that really what we're going to do is we're going to pull products off solely because you don't know the genera and species of what's in it, but it could potentially be a perfectly good allergen like lobster, and we're keeping a lot of products on the market like flowers, I guess, which probably have no role in allergic disease.

And the bar I'm proposing we set really isn't a whole lot higher than yours. You know, in

2006, the technology of developing an in vitro assay that can be used to answer a simply question, did somebody ever make IGE to something in this bottle, isn't that difficult. You know, it is very easy to set up an IGE immunoassay in vitro and the manufacturer can do this, get serum from 50 people and just answer that simple question: is there an allergen in my extract?

And that could be somewhere along the lines of basis for approval of that product.

DR. WILLS-KARP: This is Marsha again.

I guess I'm bothered, too, that there is no standardization because I worry not only about allergen deaths, but contaminants, and is that not regulated?

DR. SLATER: What do you mean by contaminants?

DR. WILLS-KARP: Well, I guess the prime example and something you work on, I know, is endotoxin or other things that may be in these extracts.

DR. SLATER: Well, I think the presence of endotoxin in extracts is well understood, and I think that, again, that's not -- again, it's important not to confuse what we're doing. This B Certainly FDA and

CBER are committed to allergen standardization, and allergen standardization is completely different from the process that we're talking about here.

In the course of allergen standardization, you establish criteria for the levels of specific allergens. You establish methods by which those allergens can be measured, and you establish potency ranges that are acceptable both from a safety and efficacy point of view.

That from a practical point of view, the number of allergens on which we can achieve that is going to be a small number in any given decade. That doesn't mean that we're not committed to the process. I think in a practical sense -- and I've discussed this with this Advisory Committee in the past -- we need to set priorities. We need to look at which allergens are of particular public health importance in order to achieve this, and then proceed on that basis.

This process --

DR. WILLS-KARP: Marsha Wills-Karp again.

I understand you're saying that that process isn't under the purview of what you're doing now, and that makes sense, but one question I have is is the standardization, the burden for that is going

to be on the FDA? I feel it should be perhaps on the manufacturers.

DR. SLATER: Well, it's a shared burden of the FDA and the manufacturers, and I think that's the way it has been, and I think that is actually a rational basis for it to be a shared burden of the two parties.

DR. WILLS-KARP: Is there a timetable for completion of standardization of a certain number of product?

DR. SLATER: Not at this point, no, there isn't. You know, the last group of products that were standardized were the grass pollens, and that was about nine years ago. We started the process of German cockroach extract a couple of years ago. We've made some very nice progress, and it's my hope that within a short time we'll have that process going much quicker.

But the efficacy review is really a separate process, and it does not involve setting minimal levels of allergens in any individual extract, and it does not involve establishing methods for measuring those allergens.

It does involve ascertaining that there actually are allergic diseases for which these

extracts are designed, and it does involve at least some evidence, some studies that extracts made from these products can be used for diagnosis and therapy.

But you know, I think what I'm hearing in the committee, and I share some of that frustration, that even at the end of this exhaustive process that has gone on for many decades there will still be less than perfect products that are left on the market.

We are, I think, certainly setting a higher standard for these products by looking for data, affirmative data that they actually are useful, are safe, and are effective, and you know, I think this is going to be an improvement in allergenics, a substantial improvement, but it's definitely not equivalent to saying that all of the allergen extracts that are out there are standardized. that would be better, but that's not something that we're doing.

CHAIRMAN BORISH: Well, maybe part of my frustration and our frustration is the point you just made, which is that after an initial slew of standardized products that got approved a decade ago, we have not seen a new standardized product in nine years, and for some reason that process has been arrested and, you know, maybe I incorrectly view it as there being an opportunity here to give B to light a

fire under that standardization process.

DR. SLATER: The fire has been lit.

(Laughter.)

CHAIRMAN BORISH: Are there any other comments from the committee members?

And if there are not, actually let me step back to an earlier item in the agenda, Dr. Slater. Let me turn the chair over to you for a second so that you can address gratitude toward a departing member.

DR. SLATER: Gratitude for a departing member.

Lynelle, are you on the line?

DR. GRANADY: Yes, I am.

DR. SLATER: Terrific. Well, Dr. Granady, I want to take this opportunity to thank you. This is going to be the last meeting that you're participating in, and I just want to say a couple of words to thank you.

You've been on this committee since February 2003. You've been involved in discussions like this last one and several other having to do with allergen standardization and with important improvements that we've tried to put into place.

The rest of you on the committee probably are not aware that I've known Dr. Granady for many

years. We go back longer than I think either of us would like to remember, but I've known Dr. Granady since she was a pediatric resident at Children's Hospital, and I have to say that in reviewing the transcripts of the meetings that you've been part of, I was impressed, and I continue to be impressed by your active participation by bringing a very reasoned voice to the meetings.

I really appreciate the service that you've put in. We all do, and we hope that you'll help us out again in the future. Thank you very much.

DR. GRANADY: Well, than you very much, and it has certainly been an honor to participate in the committee, and I'm happy to help in any way that I can.

DR. SLATER: Thank you.

CHAIRMAN BORISH: At this point we come to the part of the agenda where there is an open public hearing. I should mention that there were no prior requests from the public to address the committee, but I would like to ask if anyone present would, in fact, like to address the committee

MS. DAPOLITO: We have no requests.

CHAIRMAN BORISH: In which case we can move on to Topic 2, which is a research update of the

Laboratory of Immunobiochemistry, and I think we will have a brief break while we partially clear the room.

MS. DAPOLITO: No.

CHAIRMAN BORISH: Oh, no.

MS. DAPOLITO: Not at this time. We'll wait until these are -- there's still an open session for these two presentations, and then we'll clear the room.

CHAIRMAN BORISH: Okay, sorry.

(Pause in proceedings.)

DR. SLATER: Shall I proceed?

MS. DAPOLITO: Yes, yes.

DR. SLATER: All right. We're going to switch gears now. This is going to be a brief introduction in open session, and Dr. Rabin and I are going to give very, very brief presentations that are a small subset of the slides that we presented on June 29th to the site visit group that came here.

Again, I'm going to identify the slides. This is my research presentation, which I believe all of you have received. There are 19 slides in this presentation. Let's go to Slide No. 2.

This is a brief introduction to our research and regulatory activities. The Laboratory of Immunobiochemistry supports the regulatory mission of

CBER and FDA in assuring the safety and efficacy of allergenic products in the U.S. We do this in several ways.

We do this by performing original research, which is going to be the focus of today's brief presentations by Dr. Rabin and myself. We also do directed research projects. We provide expert advice both within our division and outside. We are very active in lot release review and in the review of INDs and biological license application supplements.

Slide 3.

Our previous site visit was in January 2002, and that was a fairly positive site visit. At the time the group said that OIB was functioning at one of its best levels in recent memory. Within the limited resources available, our lab needed to be well focused to achieve worthwhile results and the site visit committee encouraged LIB to direct future efforts and resources toward continued standardization of allergenic products.

This Slide 4.

The scientific goals of our lab are to provide insights on allergen structure and function. The connection to our regulatory activity is that this involves product, quality, safety, and efficacy.

We also characterize allergenic extracts, again, having to do with product quality, safety, and efficacy, and finally, we are very active in our work on modulation of T cell function, which is critical for our ability to review novel agents and formulations of allergenic extracts.

Slide 5.

This is our current staffing in the lab. Dr. Rabin and I are the two principal investigators. We have had two research fellows at the time, Bo Chi and Nicki deVore. The next three research fellows are listed in parentheses because even though they started recently or will be starting very shortly, they actually were not here in June when the site visit occurred, and we have three research technicians: Mona Febus, Cherry Valerio, and Katia Dobrovolskaia.

Our research program is shown on Slide No. 6, and what's appearing in red on your screen are the parts of the research program that you're going to be hearing about today. Dr. Rabin's projects are shown on the screen. He will be talking about the characterization of responses to respiratory syncytial virus by T cells, and again, in very brief summary because of time constraints.

And I will be talking about the last two

topics in my research program, which involves the potency of German roach extracts and the use of antibody microarrays to determine potency and composition of allergen extracts.

So let me talk extremely briefly about these two projects. The German roach standardization extract obviously is a very important part of our lab's activities. Three of our research technicians are involved.

In addition, we've had a very fruitful collaboration with the Intercity Asthma Consortium at NIAID, as well as with Dr. Woodfolk at University of Virginia.

The problem that we're dealing with is that cockroach allergy has been associated with asthma in the intercity. Cockroach allergen extracts are not standardized, and that standardized extracts are really needed to increase the safety and efficacy of extracts used for immunotherapy, but also that you really need standardized extracts in order to perform valid scientific studies of any extract, and so we considered it to be a high priority to standardize cockroach extracts.

Let's go to Slide 9. So the aims of the study were to establish the biological potency for

German roach extracts and to establish a surrogate in vitro method for estimating biological potency.

Slide 10.

NIAID and the Intercity Asthma Consortium were really critical in terms of getting the biological study done. They have multiple cites already selected for their studies, and it was very easy to interest four of those sites in Baltimore, Washington, D.C., Chicago and Denver in pursuing this project. They submitted an IND to support it, 11319, and the purpose of that IND, Slide 11, is to determine the biological potency of three commercially available extracts and to test their bioequivalence of the patient population who are adults with a history of allergic disease or asthma and a demonstrated sensitivity to German roach allergens that were tested.

Slide 12.

I told you this was going to be brief. The conclusions are that we determined the biological potencies. The potencies appear to be low, but in spite of that, based on existing data, successful immunotherapy dosing should be achievable.

We were disappointed that no single allergen assay would be adequate as a measure of

overall potency. We really did not find that any single allergen correlated with overall potency as measured by this.

That could be because there are other allergens that may be significant, but certainly any approach to surrogate potency testing will have to take this uncertainty into account.

The next very brief presentation -- I think it's only five slides -- this is Nicki deVore's project, "Antibody microarrays for allergen standardization.

Slide 14.

This is our effort to address one of the problems we have in addressing the potency with allergen extracts, and that is what is the best way to measure them.

We do this already by several different methods. For hymenoptera venoms, the total protein measurements appear to be an adequate reflection of allergenicity. For some other allergens, grasses and mites, we have overall measures of allergen content using cooled human antibody and recognizing presumably numerous specific allergens all at once.

And for two allergen extract types, short ragweed and cat extract, specific allergen

measurements are the best way to go, and we use sheep antibodies in those cases.

The problem that we face with this is if you look at Slide 15, in order to measure specific allergens, we need to know which allergens are relevant. That's the case for cat and for ragweed, but it's not the case for the other allergens. It's not the case for cockroach either.

However, if we measure overall potency, we are unable to detect the absence of specific and potentially important allergens. In other words, if we look at overall potency, we may get into a situation of learning subsequently that certain allergens are more important, but the overall potency measure may not be adequate to measure those specific allergens, in particular.

Slide 16.

Toward that end, we began to investigate a couple of years ago now the use of antibody microarrays to measure potency of allergens in a way that would allow us to measure specific allergens as well as overall potency concurrently. The approach is shown on this slide.

We use nitrocellulose coated glass slides, applied clonal/monoclonal antibodies as CFEs to the

slide, incubate with allergens, and then detect the allergens that are bound to the specific scFvs.

And, again, this was presented in great detail to the site visit back in June. Our aim is to develop a recombinant antibody microarray for identifying individual allergens and complex mixtures, looking at both overall potency and specific profiles, to test this method using known simpler extracts such as cat and ragweed, and to apply this to complex extracts such as German cockroach.

Slide 18.

In our studies so far we have successfully applied a phagemid library screening techniques to raising specific scFv antibodies to allergens. We have developed appropriate antibody screening methods to assess the scFvs and how they will perform in the antibody microarray platform, and we have validated the use of antibody microarray to measure the potency of these allergens.

And then finally where we are going with this is to develop a quantifiable fingerprint of complex allergen mixtures using clonal scFvs, as well as polyvalent sera and to advance to more complex allergens, specifically yellow jacket venom, German roach, and American roach.

CHAIRMAN BORISH: Questions for Dr. Slater?

And perhaps if I can being, are you concerned that your scFv approach might teach you more about immune response genes of chickens than allergenic immune response genes of humans? And had you considered maybe using, again, pooled allergic human serum and just putting IGE on your solid phase and collect every relevant actual allergen as opposed to proteins that chickens for whatever reason make antibodies to?

DR. SLATER: No, it's a good point. Not only did we consider it; we tried it, and we switched over when we really failed to pull out sufficient complexity of specific ITE encoding regions, specific human antibody encoding regions actually.

You know, I think the problem perhaps was that we started out looking at roach allergic individuals and the intensity of the immune responses were not that high in the individuals that we tried to screen. I think you're raising a good point, and that is that having successfully elicited these reactions in chickens and working with them, we now have to go back to the human sera that we've collected and verify that these are relevant responses that we're

measuring.

That being said, the power of the method is that we are really obtaining a fairly variable response in our animal model, and you know, we're certainly hoping that we'll be able to detect different profiles of the complex allergens using these multiple clonal antibodies. But you're right. We have to go back and make sure.

CHAIRMAN BORISH: So what you're saying is in the case of -- you just don't get a lot of IGE, and the IGE tends to all be against sort of a single dominant IG-1, whatever.

DR. SLATER: Right.

CHAIRMAN BORISH: Okay, but presumably the assay you have would lend itself to I think what you're saying is some kind of a rashed inhibition.

I was lucky enough to have a tour of Dr. Slater's lab earlier, and I think I did see a mass spectrometer across the hall. So what about some kind of a protein -- and I think this was in Dr. Wills-Karp's review as well. It's kind of a proteomic approach where now it takes vanishingly little amounts of protein and maybe antibody where you can sort of do a 2D separation of every protein in a cockroach and maybe pull out the ones that -- well, I guess maybe

here IGE would be sensitive enough to start pulling out different spots.

DR. SLATER: Right. No, I think that's right. I thing that is the approach that we're starting to look at now.

CHAIRMAN BORISH: Are there any questions from other committee members?

If not, then we will move on to Dr. Rabin's presentation.

DR. RABIN: Thank you, Dr. Borish.

So my work addresses the general question of whether or not viruses and, in particular respiratory syncytial virus might be an environmental factor in the pathogenesis of allergy and of asthma.

And to give that some context, I would remind what I'm sure most of you know, is that asthma really has become the classic example of an interaction between genetics and environment; that many genes linked to asthma and/or atopia are integral to innate and adaptive immunity, but that childhood exposure to house dust endotoxin can correlate with asthma prevalence and correlate with the prevalence of atopy, but in particular, the correlation with the presence of the risk for atopy is dependent upon whether or not the subjects express a known single

nucleotide polymorphism in the promoter region of the gene for CD-14, which is a surface molecule that is part of the endotoxin recognition complex, if you will.

And so depending upon the genetics then, the environment has a particular effect on whether or not a child may or may not be atopic.

Now, RSV, why would we consider RSV in particular, a viral sort of environmental factor? Well, there are a number of reasons. First of all, RSV is frequently the first pathogen that infants encounter. The T cells in infants in general are biased towards Type 2 responses and Type 2 responses are necessary for asthma.

And while we tend to focus on wheezing, asthmatics always and sometimes only cough, and that the cough likely enhances the spread of the respiratory pathogen compared to symptoms of uncomplicated upper respiratory infection.

And as such, RSV URIs trigger bronchospasm with cough and wheezing in asthmatic children, and so, therefore, really the asthma through the cough enhances RSV spread and survival.

Now, another point to be made through using RSV as a viral environmental factor is simply to

also point out that the fusion protein of RSV uses, in addition to other self-surface molecules, does signal through this endotoxin recognition complex of CD-14 and TLR-4.

Now, of course, people have looked at this correlation and asked this question for a number of years now, and here I just outline a couple of studies that are the most B , I guess, the most quoted studies, and one is the Tucson children's respiratory study, which is a prospective longitudinal study of 1,246 infants, and really came to the conclusion that differences in airway structure and multiple genetic factors may determine the development of asthma and allergy later in life, but that RSV lower respiratory infection increases the risk for an episodic wheezing associated with viral upper respiratory infections, but not true asthma or atopy.

In contrast, a group of Seegers, et al., in Boras, Sweden, looked at, has been following, and continues to follow 47 Swedish infants who are hospitalized with RSV bronchiolitis and compared with age and sex matched controls. So they looked specifically at those children who were the sickest, and these children were evaluated for asthma and atopia at one, three, and actually most recently at

about six years of age, and they find a higher incidence of asthma in the RSV group, and also a higher incidence of skin test positivity.

Well, the reasons, you can argue why would you look at the children who were the sickest, and there's actually a biological justification for doing what Seegers has done, which is that it appears that as asthma B as the genetic linkages to asthma are being determined and really verified to a much greater degree than those children who are prone to severe RSV, there's clearly some overlap in genetic linkages that make a child or a human prone to both severe RSV and to asthma.

And slide number five lists a few of those overlapping mutations, and obviously they're all associated with innate or adaptive immunity, and in particular I would call your attention to the TLR-4, again, part of the endotoxin recognition complex and part of a complex through which RSV fusion protein can signal.

And so the goals of this project have been to define the mechanisms by which RSV manipulates innate and adaptive immune responses, ultimately in the context of genotype, to find the responses of live RSV by human T cells in vitro, but in order to really

do that and to do that better than it has been done, we had to determine the cause of T cell suppression that RSV is known to induce, and in order to do that, we had to and did develop a simple and reproducible experimental model limited to monocyte-derived dendritic cells and CD-4 T cells.

And Slide 7 shows some results. These have all been published in the May 1 issue of Journal of Virology, and what we show here is that on the Y axis is proliferation in response to super antigens, staphorious endotoxin or super antigen SEB, and then on the X axis are exposure to dendritic cells with either live RSV, UV RSV and mock killed and mock infection.

And you could see that we have demonstrated here that the live RSV is necessary for the immunosuppression, which is what others had demonstrated, and so we reproduced the model, and we've also demonstrated in this that the CD-4 T cells and the dendritic cells enough are sufficient to reproduce this finding of immunosuppression.

And then on Slide 8 we demonstrate that this immunosuppression at least in part transfers with the MDDC supernatant. So here we transfer the MDDC supernatant and stimulate the cells again with staph

enterotoxin B and again demonstrate that only the RSV and not the UV RSV exposed DC is -- the supernatant from that is the only supernatant that suppresses T cell proliferation.

And cutting to the quick, we obviously looked for a panel of cytokines an did find that some were elevated, some were not, but what correlated with the findings of the supernatant findings that the UV RSV did not induce the immunosuppression, but the live RSV did was interferon alpha, and Slide 9 shows you that only from the RSV exposed MDDCs could we find appreciable amounts of interferon alpha in the supernatants.

We also looked for other species of Type 1 and Type 2 interferons, for that matter, and one that we found that was particularly interesting is a relatively newly described interferon called interferon lambda, which is actually a Type 3 interferon, and we found this by a couple of biological assays that were done by collaborators, and they're in the paper, but they're not on this presentation for the sake of brevity. And here by RT-PCR.

And so we asked the simple question whether or not blocking the receptors, which is really

the best way rather than blocking the cytokines to these interferons might reverse or abrogate the suppression that we found. So here on the Y axis now we have inhibition of proliferation. So the higher the points are, the more inhibition there is.

And on the X axis are the various experimental conditions. To the far left none of the receptor antibodies are added. In the middle section -- this is Slide 11 in the gray -- are antibodies only to one of the interferon receptors or to either of the chains of the interferon lambda receptors.

And then on the far right is the combination of antibodies to the Type 1 interferon receptor plus one of the antibodies, either of the antibodies to the interferon lambda receptor.

And what you'll notice, and we've reproduced this in a trans-weld system as well, that clearly when we inhibit the receptors to both interferon alpha and interferon lambda, we reverse and sometimes completely reverse the immunosuppression that is induced by RSV and transferred with the supernatants.

And so in summary, we found we have demonstrated and published that CD-4 T cells, dendritic cells and live RSV are sufficient to

demonstrate RSV induced immunosuppression; that the inhibition transfers with supernatant from RSV infected dendritic cells; and that interferon lambda and alpha are expressed by the monocyte drive dendritic cells in response to live virus V and neutralizing their receptor substantially reverses RSV induced suppression of T cells.

Where we're going with this is to determine the patterns of cytokine expression in response to RSV that are revealed now by neutralizing these receptors, and we're wanting to get away from the somewhat artificial system of the monocyte derived dendritic cells to look at primary myelonic and plasma cytoid dendritic cells from blood and tissue.

And in that regard, one of the things that is kind of exciting is that one member of my lab who will be joining us soon is an expert in laser capture microscopy. So we'll be able to do some in situ studies looking at gene expression in response to RSV, and I'm, in particular, very -- I anticipate some very interesting results there.

And then finally, we will compare these responses to RSV to those of other respiratory viruses, such as flu and rhinovirus and PIV3.

So, thank you, Dr. Borish. That's a brief

review of what we've done and where we're going.

CHAIRMAN BORISH: If I could lead off, first of all, I always worry a little bit about in vitro models, and I don't know, and I'm not a virologist, and I don't know how RSV works in vivo, but very specifically does RSV, in fact, infect and replicate within dendritic cells in actual people?

I know you can make that happen in your laboratory, but that's a key point because the fact that you can get them to infect and make interferon alpha is probably not by itself not a particularly surprising result.

DR. RABIN: Dendritic cells are certainly not the target cell for RSV. Okay? And in fact, we're starting to look at A-549 respiratory epithelial cells and some gene expression studies, you know, which will follow with primary cells as well specifically because we agree with you that that's not the issue.

We do, however, think that certainly live RSV makes it to the lymphoid tissues and does affect this, you know, and certainly can, you know, do this.

So we think that this is relevant, but the idea that we were focusing on the target cell, no, we're not focusing on the target cell.

CHAIRMAN BORISH: Because you may be -- well, you see the issue. An infected dendritic cell may make interferon because it has got a virus replicating within it.

DR. RABIN: Sure.

CHAIRMAN BORISH: That may not be relevant to what really happens, which is RSV components are taken up by dendritic cells, migrate to the lymph node, and present antigen arguably more to CD8 cells than CD4 cells.

DR. RABIN: Well, right, but to bring it back to the in vivo situation, you know, and to the initial point as to why we tackled this particular issue is this issue of the immunosuppression, which is known to occur with paramyxal virus. Measles is most clearly, you know, the most remarkable of that effect, but, in fact, super infections and such with RSV are known to occur, and the immunosuppression is not only CD4 T cells, but it's CD8 T cells.

So the fact that the dendritic cells would pick up the RSV and take it to the lymph node, when they arrive there, they may not function as well or, you know, the lymph node, you know, the biology within the lymph node is suppressed.

I mean, we do believe that that in vitro

finding is relevant to the in vivo clinical picture.

CHAIRMAN BORISH: But just, again, generally, immunosuppression isn't the model you're out to prove. You're setting asthma and immunosuppression is good for asthma and RSV is not good for asthmatics.

DR. RABIN: Well, okay. Your point --

CHAIRMAN BORISH: RSV is clearly, you know, stimulatory.

DR. RABIN: Right, right. Well, for the sake of -- I mean, let me state that my overall model, is that RSV molds the developing immune system of a child to serve its interest. Okay? If you will, and its interests are the children cough when they get it. Okay? And they cough more, and they get sicker with it.

Part of that molding is this mild, admittedly, immunosuppression. Okay? It may not be the thing that I would prefer to address, but in order to address it, in order to address what RSV does, okay, better than any of my competitors, I have to address this issue first. Okay?

The final thing is that part and parcel of that model is that not all children -- and it's not necessary that RSV do this to all children -- that RSV

probably capitalizes on the subset of children who are more prone to atopy and asthma by virtue of the single nucleotide polymorphisms that I showed on the slide.

So the immunosuppression is something that I would actually rather not have to deal with, but in order to ask the other questions, I have to answer that one.

CHAIRMAN BORISH: Questions from other members of the committee?

Let me repeat that because we had turned the volume down to knock out some of the background noise. Were there questions from other members of the committee?

DR. ATKINS: Dan Atkins. I just wanted to ask about the 47 Swedish infants. When they look at that was the family history of atopic disease higher in that group than the general population?

DR. RABIN: I believe, Dan, that it wasn't. I believe I would have to go back and look at some of the papers because certainly that's in there, but I believe that it wasn't, but as I remember the case controls were SIPs. So they kind of took that into account in any event.

DR. ATKINS: And that was the other question. When they matched for agent, did they match

for family history of atopia as well?

DR. RABIN: Yes, I believe that they did. I mean, I think that they did the study as well as you can do a study with case controls, which is to say that it's flawed because of case controls, but they tried to control pretty well, and of course, they're dealing with a more homogeneous population in general than, say, a comparable American study would be.

DR. SHEPHERD: This is Gillian Shepherd.

One general question. Have you looked at your monocyte derived dendritic cells in your CD4 positive T cells and genotyped them? Because there clearly is data about differential reactions pending the genotype. I noticed actually there was an article in September JSEI showing exactly there are some cases of exposure to farm bacteria with the development of atrophy.

DR. RABIN: We haven't, but --

DR. SHEPHERD: With CD14.

DR. RABIN: Yes, we haven't, but we're planning on it. I mean, we're planning on a number of studies in the genotyping in particular that I'm very interested in doing on all of our donors, is the TLR4D299G. We need to know that for all of our donors, and I intend to do that.

CHAIRMAN BORISH: If there are no other questions, then I guess we will move to closed session, and we'll take a one or two minute break during which time I will apologize for trying to throw Dr. Rabin and Dr. Slater out of the room before their presentations, which clearly went a lot better with them actually here to give them.

(Whereupon, at 2:18 p.m., the open session of the meeting was concluded, to reconvene immediate in closed session.)