arbitrary, but we would certainly like to get an idea across the industry as to what was going on with this particular product.

We would also be interested at that point in receiving products from other sources, from academic laboratories that study the particular product, from the NIH, from industry R&D departments and we also reserve the right to make our own product if, for some reason, we are not fully satisfied with what we are seeing.

We would then do a series of comparisons among the products. We would have to develop and adapt methods for allergen determination. We would compare the allergen content of the different lots and then this part sort of then feeds back into the impact criteria. If, for instance, we find that everything is remarkably consistent within the industry, we might wish to reconsider the impact or, better yet, if the commercial products are somehow comparable to the best material that we could get from, say, an academic lab or from other sources, then, again, we might reconsider the impact.

But, again, this decision would have to be taken fairly carefully based on some analysis and understanding of what is actually going on with the allergen and how good the allergen is out in the market. In the clinical phase, Phase 2, we would initiate some

clinical testing. Very likely, the predominant testing would be intradermal skin testing by the model that has been used extensively, although it is possible that histamine release data might be used and, furthermore, it is also possible that some limited immunotherapy data might be sought in terms of helping us to establish biological unitage and ideal dosing ranges.

One important dropout point here is that let's just say that we discover, based on the clinical testing that there is almost no evidence that this material is related to IgE mediated disease. It is a possibility, after all, that we have to entertain.

So, not only would we be willing to reconsider the impact of standardizing and stop the standardization effort, but we really need to take it a step further and consider getting this product off the market entirely. So, withdrawing our standardization effort is sort of a -- you know, a little bit of a carrot and a little bit of a stick as well. But we need to be open to the possibility that we will learn as a consequence of our studies that Product X really shouldn't be offered in either standardized or under unstandardized form.

Now, moving on to the bottom part, the manufacturing phase, the idea here is to move into the real guts of how we are going to regulate the product and

that is to develop in vitro surrogate testing. As you can imagine from the first hour or so of my talking this morning, I am open to any kind of testing that would be a good surrogate.

Based on previous experience, it is likely that immunologic testing is going to end up being the best surrogate, but it may be, if we are very lucky, that we could use some physical, chemical methods that would be a good surrogate. By "surrogate," I mean, it would have to correlate to the clinical testing that had been done in the previous phase. We would then select the provisional reference standard.

This would be validated for testing and the standard would be validated by CBER and industry and then finally at the end of this phase, we would select the reference, establish release limits and initiate stability testing. In the post approval stage, we will continue the stability testing, initiate safety monitoring of the products and then we would start to look at equivalent dosing.

Remember, we were talking about earlier -- what Rich Pastor was talking about earlier, about using clinical data to establish release limits. Certainly, in the absence of clinical data, we would want to use the best, most accurate testing available. But once clinical

data start to accrue with particular allergens, we would definitely be open to the possibility of looking at equivalent doses and establishing the release limits or modifying release limits based on that knowledge.

So, that is the algorithm. Let me just make another general comment about the algorithm itself before we go on to specific allergen standardization targets. The algorithm is not contract precise. It doesn't tell us exactly what we would do in every single situation. The function of the algorithm, as far as I am concerned, is to enshrine what is essential about standardization and not let go of it. And, yet, to be flexible enough to deal with a whole variety of standardization issues that may well come up as we look at a new generation of products to standardize.

It is not clear what surrogates we are going to use. We won't know that until we actually look. It is not even clear necessarily what best clinical tests are going to be to use, although certainly our initial bias will be to use the intradermal skin testing, since we have so much experience with it.

Yes, sir.

DR. CLAMAN: On a crass commercial level, who is going to do the clinical testing and who is going to pay for it?

DR. SLATER: That is not a crass commercial question at all. It is a very good question.

I am actually going to defer the answer to that question a little bit until I finish the next part of the talk because I think it will come in relevantly. The short answer is we could do the testing. We could pay for the testing or we could contract out and have the testing done elsewhere. The advantage of contracting out is that we do want to make sure we have some geographical diversity in the individuals that we test. So, we would have to do at least some contracting out and we are prepared to do that.

I will put off the who is paying for it for just a minute if you don't mind. So, what we really want to do is really want to enshrine the best about standardization without fossilizing the process. I really wanted this to be -- and the consensus among the group that we wanted this to be as flexible a process as possible, but, in addition, giving us guidelines as to where to go.

In terms of specific next standardization targets, I just want to review briefly what this committee -- the discussion this committee had in the 1998 meeting at which potential next standardization targets were discussed. At that time, the allergens that

I have up on this slide were prioritized roughly from high to low in terms of next possible targets. They included latex, cockroach, tree pollen, peanut mold and dog.

A new element has come into our discussion of standardization however and that is the strategic plan of the Department of Health and Human Services, dated March 1999, entitled "Action Against Asthma." Now, this is a strategic plan by DHHS that was initiated sometime before at the request of Secretary Shalala, who had identified asthma as a major public health concern of the people of the United States.

Toward that end, a large group of people, among them, CBER was represented by Dr. Paul Turkeltaub, a large group of people from DHHS got together to formulate a plan to go forward and see how the Department was going to deal with the problem of asthma in the United States. Clearly, NIH, FDA and CDC are playing lead roles in this strategic plan.

Under Dr. Turkeltaub's guidance, the group recognized explicitly that allergens played an important role in asthma and that allergen standardization clearly played a role in the improved treatment of asthma in terms of the improved diagnosis, allergen avoidance, better safety and immunotherapy and, lest I beat on this

horse anymore, better science with the effort of standardization.

We know that allergens and asthma are connected. The case is strongest among the indoor allergens. The case is strongest still among two indoor allergens that have already been standardized, the dust mite allergens and the cat allergens, but there are very compelling arguments to be made for the role of cockroach, molds, dog and even some outdoor molds in the etiology of asthma in certain children and adults.

We were asked to come forward with a standardization proposal in response to the asthma initiative and this is the proposal that we have put together subject to the comments of the advisory committee. That proposal is over the next three to five years to standardize cockroach, aspergillus fumigatus and alternaria alternata as three potential choices in response to the asthma initiative.

DR. SAXON: Which cockroach is it? There are more than one of them. Are you talking about several species?

DR. SLATER: Yes. I am talking about several species.

I am sorry?

DR. SAXON: Two or three?

DR. SLATER: Well, two or three. So, the wateladramatica(?) and the paraplanata(?) mericana(?) are the two major ones.

DR. SAXON: The list is actually a little bit longer because --

DR. SLATER: That is right.

But certainly cockroach is ubiquitous. It clearly is associated with asthma, especially inner center asthma. If there is one lesson that I have learned from the inner city asthma study it is that you can't eradicate cockroaches. It is one of the most dramatic scientific results of the inner city asthma study is that you can kill them but you can't reduce the allergen exposure.

So, I don't know how many of you heard Payton Eggleston(?) make his presentation last year about their efforts to eradicate cockroaches, but it was rather strikingly depressing. So, if you are going to control the problem of the immune response to cockroach as a possible etiology for asthma, it seems to me that immunotherapy is an important way to go and if we are really going to learn anything about it, we need to standardize these allergens.

As you said, there are several species that are known and several cloned allergens as well. So, it seems

to me to be a reasonable target. Aspergillus fumigatus is a fungus that grows in both and the outdoor environment. It is clearly involved in several allergic or hypersensitivity diseases. It is involved in certain forms of allergic asthma, allergic sinusitis, allergic bronchopulmonary aspergillosis, as well as hypersensitivity pneumonitis, particular molt(?) worker's lung.

So, clearly it is an allergen that is important. Several allergens from aspergillus have been cloned and, again, it seems like a reasonable target in terms of asthma.

Alternaria alternata is mainly an outdoor soil allergen. It is highest in the grain-producing states. There have been striking reports of fatal asthma associated with exposure to alternaria allergens. Again, alternaria has been -- many of the allergens have been well characterized and it seems like a reasonable next target for allergen standardization in response to the asthma initiative.

So, again, in response to the asthma initiative, which as you can imagine has some funding attached to it and so it is something that can help us more forward rather quickly with this, we have tentatively proposed to go forward with the

standardization of cockroach, aspergillus fumigatus and alternaria alternata.

We are now a minute late for our break. But I am just going to take about 30 seconds more just to review the three questions that we are going to ask the committee to discuss in the discussion session this afternoon.

Question No. 1: Should CBER expand the lot release limits for standardized mite and grass pollen allergen vaccines to 0.5 to 2.0, as described in the draft "Guidance for Reviewers, Potency Limits for Standardized Dust Mite and Grass Allergen Vaccines: A Revised Protocol"?

Question No. 2: Should CBER implement the proposed algorithm for the standardization of new allergens?

Finally, Question No. 3: Should cockroach, alternaria alternata and aspergillus fumigatus be selected as standardization targets, given the support of the DHHS asthma initiative?

DR. OWNBY: Are there any immediate questions for Jay before we take our lunch break?

DR. SAXON: Are we going to have a chance to question him in the afternoon?

DR. OWNBY: We can grill him all afternoon,

yes. We will also have time for comments from other interested parties that may pertain.

Okay. Then I think we have an hour for lunch.

[Whereupon, at 11:38 a.m., the meeting was recessed, to reconvene at 12:40 p.m., the same day, Thursday, February 10, 2000.]

A F T E R N O O N S E S S I O N [12:40 p.m.]

Agenda Item: Open Public Hearing

DR. OWNBY: The committee is now open for public comment on any of the matters that were on today's agenda and I would encourage any members of the public or industry that would like to address the committee to let me know and we will take each of you in turn.

I am hoping we don't have to worry about any major time constraints on that. The committee does have, as proposed previously, three other items to discuss that are related, but let's have public input first.

Yes.

MR. HAUCK: Thank you, Dr. Freas, for the opportunity to speak today. I will be very brief.

I am Peter Hauck and I am the president of the APMA. The APMA is the Allergen Products Manufacturers Association. The APMA is a non-profit trade association. It consists of nine member companies, as well as eight associate members. That is, the nine member companies are all of the nine U.S. licensed manufacturers of allergenic extracts.

The associate members are other North American and European manufacturers and distributors of allergenic extracts, as well as raw material suppliers. I provided the committee a list of our members, which is this

document here and the last page are those of us who are foolish enough to be officers of this organization.

Our association was started in 1987, recognizing the need to cooperate on issues that affect our industry, primarily dealing with scientific and regulatory concerns. Our members meet regularly with FDA to participate in workshops and meetings, to exchange data, information and perspectives on various issues associated with these allergenic products.

We have also provided speakers and sponsored workshops in seminars on immunotherapy and allergen standardization at both the academy and college meetings. My sole purpose in being here today is to just tell the committee, let you know that we are a resource for you. Understanding that there are two sides to every coin, we encourage you to contact us on issues that may come before this committee.

In that regard, I have also made a list of the various interest committees that we have in our organization with the individual chairpersons of those committees, along with their affiliations. Feel free to contact them directly or any member of the executive committee.

That is really all I had. I am prepared to answer any questions that the committee may have on our

organization or any particular position that we may have on any issue. That is all.

DR. OWNBY: Are there any questions for Mr. Hauck?

DR. SAXON: How long have you been involved with this committee, the APMA?

MR. HAUCK: Since it is -- me personally?

DR. SAXON: Yes.

MR. HAUCK: Since its inception.

DR. SAXON: So, what do you think -- I mean, there have been some change now. I have only been a member of this committee for a couple of years. What do you think of this change? How do you think it is going and what --

MR. HAUCK: I think as far as the allergenic -- the Laboratory of Immunobiochemistry -- those folks over thee, I think they have -- the last three or four years have made really remarkable progress. They are a very good group of scientists, good people, very open dialogues.

We support most of their work. We may have issues, some regulatory issues that we take issue with. We may have some logistics problems, but by and large we are very supportive of it.

DR. SAXON: You think the industry is pretty

much on board on this standardization stuff?

MR. HAUCK: Yes. We absolutely support the standardization of allergenic extracts. On the other hand, there may be logistical issues or regulatory issues with that that we may not necessarily agree with.

DR. CLAMAN: Would you like to give me an example of a regulatory issue on which you don't agree?

MR. HAUCK: Sure. How standardization is implemented can be an issue. In other words, if it is considered a change in the regulations, there should be ample time for notice and comment. And there are issues, regulatory issues that surround this that I would rather not go into that are part of the citizen's petitions. That is an example of a regulatory issue.

A logistical issue might be something like, well, we don't have enough of this reagent or we keep changing reagents and how does that affect our stability studies? So, those are some examples. Does that answer your question?

DR. CLAMAN: I guess.

DR. OWNBY: Do you have a follow-up question, Henry, or --

DR. CLAMAN: No.

DR. OWNBY: Sam.

DR. LEHRER: With regard to the standardization

of allergenic products, Jay had mentioned a couple of products that they were proposing for standardization. From your perspective, from the industry's perspective, do you have -- I think you have a pulse on what the public uses the most and what is not standardized.

MR. HAUCK: Yes. I think we should be part of this equation, part of the algorithm. Again, we are a resource not only to the committee but also a resource to FDA as far as maybe getting some input on what are widely used allergens.

Beyond that, I think, not necessarily speaking for my organization, but in the general sense, looking at these group of three allergens, there was an initiative four or five years ago with cockroach, where a couple of manufacturers got together with FDA, developed some serum pools, started the standardization initiative and that kind of fell short for a number of reasons.

So, I think most of the manufacturers, since they have -- many of them have developed serum pools have maybe internal reference preparations. This might be an easy one to standardize. As far as the fungi go, that might be biting off a bit more than you can chew. I would encourage you to come up with a backup plan in case the alternaria and the aspergillus don't work or if it seems to be a little tough.

I know a lot of the manufacturers, for example, have birch(?) systems. Certainly, Sam, you have got a shrimp system and there is probably, you know, some kind of good reagents for standardizing peanut. So, those are all things that maybe you want to -- you know, that you really talked about, Jay, as part of the equation.

I just get concerned when I see molds up there for standardization. That is a tough one.

DR. SHAPIRO: I hear rumors being spread about companies dropping out of the antigen manufacturing business and also about the withdrawal or the lack of availability of more and more allergens. Again, I don't have any specific source but there is some concern in the allergy community. Could you tell me something about what that means?

MR. HAUCK: Sure. It is not a rumor. It is true. It becomes increasingly more expensive to produce these allergens. That is one part of the equation, to keep them in compliance with what you would do with making an injectable drug. I think it is clear that we have to manufacture these products to a higher standard than we have in the past.

So, that takes a bit more money. In the sense that there are fewer allergens, yes, manufacturers have looked at their product line and say, well, I can't make

night blooming jasmine because I sell three vials a year and it costs me $2,000 to make it.

So, sure, we are all trying to limit our product line to those items that are more common. Another problem, which is a little more complex is there are fewer and fewer collectors of these source materials. Because the price of these products has been depressed, it is very difficult to convince somebody to go out and collect pollen because it is a very tedious job and it involves some art as well as some science.

So, the pollen collectors that are out there, the major firms that are pollen collecting companies are going to concentrate on those products and those source materials they collect well and that they can collect and make a buck on. So, there are -- it is going to be more and more difficult or perhaps more and more expensive to purchase some of the more less commonly used items.

Now, it doesn't mean that they are important. They could be very important to a few of your patients and certainly a hundred percent of one patient is very important to that one individual. But option may not be available anymore.

I have some colleagues -- am I speaking correctly?

PARTICIPANT: Yes.

DR. SOTO-AGUILAR: I would like to know the process of development of any allergen extract in the manufacturer -- I was involved with the skin testing for standardization of one of the extracts a few years ago. So, I became familiar with, you know, the skin testing method by Dr. Turkeltaub and I found it extremely interesting and very effective, but I would like to know what is the time line that you have.

How do you come to have the ideal solution for certain allergen? Then at which time is that allergen presented to the FDA for skin testing? At which time is that lot selected and then sent for review and how much volume do you have of any particular lot that eventually if it is approved, will be available. I mean, what is the process? Is there any way to know about it?

MR. HAUCK: I think the process of standardization in general is more or less left to FDA and it is a consensus. They more or less -- we get together and see -- you know, they tell us what the allergens are and then we see if we have the reagents to develop and it is a collaborative effort.

Skin testing is certainly part of that. That is the in vivo part. But the initiative can come from industry. It can come from FDA. It can come from the allergist community. So, I don't know --

DR. SOTO-AGUILAR: And then once a lot is approved, how much volume do you have at least a minimum in order to be feasible to be marketed, a lot in volume and, you know --

MR. HAUCK: Well, a lot could be -- it could be -- after the testing is done, it could be one vial. I am not sure exactly what you were getting at.

DR. SOTO-AGUILAR: No, I am talking of the manufacturer, how much volume of that particular lot or batch will be available if it is approved, if it passes all the standards?

MR. HAUCK: The amount of product that is sent out for lot release is minimal. It is 20 or 30 mls. So, it is whatever the manufacturer's batch size is, based on his projection or his market forecast for his percent of the market. So, it could be a 5 liter batch. It could be a 10 liter batch. It could be a 20 liter batch. It could be a 20 liter batch. It could be 10 vials, a hundred vials or a thousand vials or maybe 2,000 vials.

DR. SOTO-AGUILAR: There are no set limits for that or minimum?

MR. HAUCK: No. There is no minimum. There is, obviously, an economic minimum. I mean, I am not -- our company is not -- my company is not going to make two or three vials of something because by the time we are

done with all the testing, those vials are going to be very dear to us because of the amount of labor and overhead into that.

So, I guess I am not answering your question.

DR. SOTO-AGUILAR: Maybe I am not expressing myself well.

We talked about how many lots were tested. Seven --

MS. BLOOMER: My name is Diane Bloomer. I am with ALK-Abello. Maybe I can give some clarification here.

I think, Peter, you are talking about existing standardized products and what we have to go through. And you are talking about how we would get a new standardized product or even bring a new product that is neither standardized nor non-standardized to market.

DR. SOTO-AGUILAR: Just a new product. I mean, or a new batch or whatever is being tested, like the 477 lots that were tested in 1999.

MS. BLOOMER: Those were standardized products.

DR. SOTO-AGUILAR: They were standardized, but do they represent large volumes of batches?

MR. HAUCK: Generally, they do.

MS. BLOOMER: Yes. They usually are fairly large size because we send in a specific amount to the

FDA for their testing and then the remainder of it is for our stability studies and then for marketing.

DR. SOTO-AGUILAR: Which is the minimum that you have to have for any particular --

DR. SAXON: There is no rule about that and no one has suggested there ought to be a rule.

MS. BLOOMER: We don't want a rule.

DR. SAXON: It is the manufacturer's business to, you know, take care of how many -- whether they think there is going to be 10,000 vials of fahia(?) grass or 1 vial of this. I mean, that is a marketing decision.

PARTICIPANT: -- straining the resources of FDA by the lot release --

DR. SOTO-AGUILAR: I am just thinking on the physician using the lot, buying the lot and having comparable lots to using the patients. Like if I buy it now and then I buy it in six months and then you have got to -- we are always going to be talking of different lots.

DR. SAXON: That is why the FDA standardization program exists, so you don't have to worry about that, so they don't have to make one huge lot to last ten years.

MR. HAUCK: If you have a standardized product and if we look at the data we saw today from Dr. Pastor, it shouldn't really matter whether it is lot A or lot B.

If you do some, you know, maybe some minor dosage accommodations, going from lot A to lot B, but essentially when you prescribe a medication to a patient, you don't worry about what particular lot that patient is getting.

So, I think the idea with standardization is -- at least the philosophy is to have some confidence that the product you are getting meets a certain standard of potency and it is more or less interchangeable from lot to lot, at least from the same manufacturer.

DR. SOTO-AGUILAR: Right. I have that very clear in my mind and that is the reason we are here. It was just for -- I was talking in the long term basis. We are talking of lots that, hopefully, will be stable for ten years.

MR. HAUCK: Those are references. Those are not --

DR. SOTO-AGUILAR: Those are the reference. Okay. All right. Thank you.

DR. WRAY: I would just like to raise the question of latex again. I understand it is not one of the priorities with asthma, but still is an important allergen that we need in clinical practice. I wondered if any of the manufacturers are close to having a standardized product that might mean that we really

should push on with that. That may be --

MR. HAUCK: I can only tell you what I know. There is one manufacturer that is involved with latex and they have done clinical trials. They have done a lot of work with it. If it is licensed and approved, it should be commercially available.

DR. SAXON: I don't think the manufacturers -- I think we need to address those questions to the FDA personnel if you want.

DR. WRAY: Well, it has to do with the priorities, though, as to what is going to be next on the plate.

DR. SAXON: I don't think this gentleman is in the loop on that.

MR. HAUCK: I don't think I should be.

MS. BRIDGEWATER: [Comment off microphone.]

MS. LIBERA: Have you projected the type of savings that manufacturers would have with reduced lots that were thrown away?

MR. HAUCK: With Dr. Pastor's suggested changes, certainly there would be some savings. It just -- but I personally or my company were -- as far as I know, the industry has not projected that. But it just makes such imminent good sense in my mind. I haven't really looked at the economic end.

DR. OWNBY: Do you think you could give us an estimate of the economics? Are we talking hundreds, thousands or millions of dollars?

MR. HAUCK: If you throw out a batch of mite, it definitely gets the attention of the accounting department. The source material per mite is about four times the price of gold. You might remind your patients of that, too.

DR. OWNBY: Dr. Claman.

DR. CLAMAN: Mr. Hauck, you mentioned something about a citizen's initiative. Is that the asthma initiative that you were talking about?

MR. HAUCK: No. This is a legal thing. This is what is called a citizen's petition.

DR. CLAMAN: And what does it say?

MR. HAUCK: It is a rather document drawn up by a lawyer. It deals with two issues, the logistics of standardization and it deals also with the way standardization is done.

DR. CLAMAN: Does it deal with matters that we are discussing at this meeting?

MR. HAUCK: I don't know that it is terribly relevant to what is going on at this meeting. It deals with more of the regulatory concern about notice and comment when you make a change in the regulation. It is

the perception of the majority of the membership of the APMA that when you standardize a product, how it is standardized and so forth, it should be in the Federal Register, but that is not why I am here today to discuss this -- that topic.

DR. CLAMAN: I gather that you as representing the manufacturers are not overly enthused about a mandate to do molds and to standardize molds. What I would say --

MR. HAUCK: I would love to do it. I am just saying I just think it is very difficult.

DR. CLAMAN: Well, I would say -- I am not a chemist and I have forgotten most of the formal talks that I have listened to in the past x, y, z years, but I remember one a few years ago about mold allergens. I came away from that talk, which was a very good one, and said to myself, my God, this is impossible.

DR. OWNBY: Other questions?

Thank you very much.

MR. HAUCK: Thank you very much.

DR. OWNBY: Are there any other persons who would like to make comments to the committee on any of the issues for today? No one? Okay.

Agenda Item: Committee Discussion

We were asked earlier today to make

recommendations on three different issues. Those are in your agenda. The first one specifically is whether CBER should expand the lot release limits for standardized mite and graphs, pollen allergen vaccines, to 0.5 to 2 as described in the draft Guidance for Reviewers, Potency Limits for Standardized Dust Mite and Grass Allergen Vaccines: A Revised Protocol.

Is there discussion on the committee of any of the other issues or any questions you would like to address to Dr. Slater or other -- the people who are here about that draft or the rationale behind it or the implications?

I was asked that we actually take a vote on this issue at the conclusion of this as a committee, but remembering that we are an advisory committee to the FDA.

Dr. King.

DR. KING: Dr. Pastor said it doesn't matter whether the relative potency varies by a factor of 4 because you will not detect an adverse reactions or affect its immunogenic efficacy. That very well is true; that is, whether you immunize somebody with 1 microgram or 3 microgram, you would probably get the same result.

But still from the point of view of regulation, wouldn't you try to say that this batch of insulin has 5,000 units instead of 5,000 to 20,000 units? I mean,

that we should try to be able to state that in a little bit narrower range. I understand where he also pointed out the amount of work involved. To me, it is just sort of making it too -- perhaps ELISA inhibitions kind of draw all these curves to make it parallel and everything, but with some -- let's say if you are talking about some allergen has an enzymatic activity, you can easily measure very reliably.

One should be able to cut down the standard deviation.

MS. DEAL: My name is Carolyn Deal, for those of you who I haven't met before. Maybe I could put what we are talking about in a bit of a perspective compared to all of the other biological products that we regulate. One of the things I think we are trying to do with this is this is not in the situation where we are evaluating, say, patients in a clinical trial or not. Now we are looking at evaluating manufacturing and consistency of manufacturing.

I don't come from an allergenics background but from a vaccine manufacturing background and this is very similar to the types of problems we deal with in that arena. Ideally, correctly, you would like to be able to manufacture something exactly the same from lot to lot to lot. But as you know, that is impossible in a

manufacturing facility. So, what we are trying to do is balance the inherent variability so that we minimize as much as possible in manufacturing. Yet at the same time, maintaining the potency and safety of products within a limit.

What I would say is the perspective is in all biological products we have limits. There is nothing -- we can't say an absolute every time. And if you go back, say, and look at the things that you look at for vaccines, all of those also have limits.

So, I think part of this is in the perspective of treating these products the same as all of our other biological products and maintaining the public health, safety and efficacy of the products; yet, at the same time not putting undue burdens on the manufacturing. As we look at all of these with biological assays, there is inherent variability in a biological assay, that the more repetitions you get, you can get to the point of diminishing returns.

So, just as a perspective for this discussion for these products, compared to all of our other products.

DR. PASTOR: Really that is -- don't forget, their actually was a sequence of events where there was the skin testing. After the skin testing got the

standard of 100,000 BAU, the next step was to validate the ELISA, such that it gave the equivalent potency.

So, then, therefore, because the ELISA is a test, we had to live with the variability of that test. Now, if, in fact, we had then done a protein test and the average value of the protein test was exactly the same as the value of the ELISA test and the protein, as you know, is a much more precise test, then we would do exactly as you suggest. We would base the limits on the protein test and, therefore, make it like narrower. So, continuing with the protein example, as you saw, for the same value of the ELISA, the protein varied by a factor of 10. So, that like didn't work. If you were to find another test such that it gave the same average value as the ELISA and was much more precise, sure, we actually would switch.

But since we don't have that, yet, we have to do something and as Mr. Hauck said, every time they like reject a lot of mite, it is actually quite a lot of money. So, we have to ask very carefully is it appropriate that the FDA put that burden on the industry that they have to reject of mite.

So, coming back to it, I think, in the future we will have tests that are more precise and when we have such a test and it is validated, we will switch to the

more precise test.

Does that answer your question or maybe Jay would like to add something.

DR. SAXON: I accept the variability in ELISA's. I unfortunately have to live with them and they are very uncomfortable and that leads to some of that imprecision, which isn't a manufacturing issue, I feel. And I understand that.

What happens -- I don't quite understand. If you get a lot that is submitted as a 1, right, and it comes out as a .6, which is fine, right, and you get another lot that is submitted as a 1 and it comes out as a 1.8, which again it is fine. When they actually labeled by the manufacturer, does this label it as a 1? Does it label it as a .6 or does it label it as a 1.8, meaning do they actually go by the number? I just want to know the answer. There has got to be an answer.

Do they label them as a 1? They get labeled as a 1. Okay. So, within that limit, they get labeled as a 1. I understand. Fine.

You don't need to explain it. I understand. I just wondered how it worked. It is fine.

MS. LIBERA: So, the lots are labeled whether they are high or low?

[Multiple discussions.]

DR. OWNBY: Let me state this. I think I am correct. You can correct me if I am wrong, that if they fall within the acceptable limits, they are labeled as 1 and that is usually a hundred thousand or 20,000.

MS. LIBERA: So, they can fall in the larger range and still be labeled --

DR. OWNBY: They all receive the same limit as long as they are within the range.

MS. LIBERA: Does it matter to a patient who is on therapy whether they --

DR. SAXON: The problem is the variability of the assay is such, you are not really sure that your .6 is really not a 1.

DR. CLAMAN: And then the variability of the patient's response is shown by those dose response curves, which are rather flat. Now, we are concerned with safety. Obviously, that is the problem. And we all know on a practical basis that the main safety problems in the delivery of allergenic extracts have nothing to do with the manufacturers at all.

It is the nurse who picked up the wrong bottle or the pharmacist who mixed it wrong. Now, we are not discussing those things and there isn't anything we can do about it here, but neither can the manufacturers and neither can the FA. So, I think the fact that the dose

response is rather flat is lucky for us and lucky for the patients that there is a built in safety factor, which includes some of this variability.

Dr. King is coming right to the microphone because he is a chemist and he is going to kill me.

DR. SLATER: I would just like to recall for the committee two fundamental parts of the analysis. One is we are doing absolutely nothing to change how the manufacturers select and screen the materials that they send to us. The materials still have to observe the old release limits, which are basically statistical identity to reference. Okay? Those release limits are statistically indistinguishable, based on the test to reference.

The proposal merely changes the way we handle materials that are truly at those statistical limits and how we are going to handle them; whereas, in the previous system, the current system, a material at the reference limit would have essentially a 50 percent change of failure, was the example that Rich gave.

Under the proposed system, it would have something less than a 50 percent chance of failure, depending on the number of replicates, in other words, the reliability that the manufacturer gave us with the number. The second important part of the analysis to

recall is our analysis of the ranges, of the predictable ranges of potencies of two randomly selected materials taken out of the distribution of a particular product.

Remember that that predicted range, either the mean range or the 95 percent maximum range, is purely a function of the sigma. It has nothing to do with the limits that we pick or that we set. It is a function of the distribution, i.e., the narrowness of that curve. The narrower the curve, the less likely there will be much of a variation.

In fact, based on the data that we were able to collect, really in the end from nearly 200 lots of material, it was fairly reassuring in that sense. It said that over 95 percent of those random changes are going to be less than 80 percent off from each other, well within the fourfold, actually within the current limits as they currently exist.

So, in fact, my estimate is, although this is, I think, conceptually an important change, it is going to be practically of limited significance, except that we are going to be treating those extracts that are on the edge in a statistically valid way. Whereas, before, we really weren't.

DR. OWNBY: Dale, go ahead.

DR. UMETSU: So, my understanding is that if

there -- the manufacturers are not going to be changing their procedure. So, when they do ELISA assays for each lot, they do it six times. Is that correct?

DR. SLATER: Some 3, some 6.

DR. UMETSU: And there is no way to standardize that. Why are some 3 and why are some 6?

DR. OWNBY: Isn't that the manufacturer's gamble, that the more times they do it, the more it costs them, but the less likely they are to get a lot rejected; whereas, if they cut back on the QA, they are more likely to get a rejection. So, it is a statistical gamble one way or the other.

That is a manufacturing choice. That is how you design your business.

DR. UMETSU: But isn't that this new proposal, though, assuming that the manufacturers have a fairly good quality assurance? So, wouldn't 6 be better than 3? It doesn't make a difference?

DR. SLATER: It is part of the license application.

MR. HAUCK: Most manufacturers are using 6 now and maybe it is not mandated, but certainly when FDA reviews a license amendment or in the standardized grass program, the suggestion was made by FDA during reviewing of these licenses, hey, guys, you know, your numbers were

kind of all over the place, as Richard pointed out earlier. How about more replicates during a point in manufacture, either in final containers or in bulk. That is what manufacturers have done to reduce -- to be more consistent, not only from an economic point of view that you don't throw product out, but even a manufacturer is going to have tighter limits than its release limits.

If I have an experience of .8 with a specific raw material in my method of manufacture and all of the sudden I come up with 1.3s, that is within the limits, but certainly as a manufacturer, you get a look at that. Okay? So, in essence, FDA has kind of guided the manufacturers into more replicates and, in fact, most of us do use 6.

DR. OWNBY: Other questions from the committee?

DR. WRAY: I was just going to make a comment that I think we need to keep in mind the importance of allergy causing asthma and that there are so many patients, who cannot afford the benefit of allergy extracts and that unless we have some overwhelming reason to think safety is an issue, that we should try to remove any obstacles to providing more extracts to people.

DR. OWNBY: Jay, it seems to me that if I was a manufacturer in business, I would try to optimize my profit and if I was extracting material that was four

times the price of gold, I could have someone calculate for me the odds on rejection and I could add excess water to my extract and deliberately produce an extract at .8 reference or .75 reference and figure out what the probability is that I am going to get a rejection from the FDA, when I am deliberately at that level. With this broadened limit, it is going to allow me more freedom to do that.

DR. SLATER: We actually can look at that and we can continue to look at that. It is part of our analysis of the standard distribution of the products. We looked at the failure rates of the products and we were pleased and reassured that the distribution of failures was roughly even high and low. Had they all been low, I think we would have been suspicious about what what you said, but the fact that the distribution of failures was evenly distributed -- and, again, there weren't that many failures but the distribution of failures was evenly distributed -- suggests that the current manufacturing practice is exactly what we intend it to be and that to aim at identity to reference for a relative potency of 1.

I think we would --

DR. OWNBY: What about next year if the relative potency on the average lot of mite is .8 instead

of 1?

DR. SLATER: Right. We will know.

DR. OWNBY: But would that give you -- is there any regulatory way to say to manufacturers that something has changed and we are concerned about it? I mean, there are still -- the majority of their extract is going to meet specification.

DR. SLATER: Right. I think first of all, even though we will have broadened the limits that we use for failure, they still will be increasing their chances of failure by going low. If you look at that table that is included, the failure rates are lowest at a relative potency of 1. So, if a manufacturer really wants to minimize its chance of failing, they will continue to aim for a relative potency of 1 and we fully expect that that practice will continue.

If, however, they make an economic decision to balance it off and aim for something lower, the failure rates will go up even by our method and, furthermore, their failure rates will go up asymmetrically and we will be tracking that and looking at it.

Whether we have an explicit preexisting mechanism to jump in and try to rectify that, I have no idea, but I certainly would look for hard for one.

MR. HAUCK: First of all, you have given us a

great idea on that. The other side of the coin, why a manufacturer wouldn't do that, we put one lot -- you have to put these on stability. So, if your products at or near the limit during its shelf life, it is going to fall out. If it falls out, you have got all kinds of issues going on. So, the manufacturer, trust me, wants to be as close to 1 as possible.

DR. PASTOR: It is also pretty hard to nail it down.

MS. BRIDGEWATER: I wanted to point out, Peter, to even say this, but the formulation is not that precise. I think the way that I have seen -- when you are formulating, you always target 1. It is not so precise that you can kind of monkey with the numbers to shoot for an 01. It is too difficult. I don't think you could even do it practically. It would be very difficult.

DR. OWNBY: I think they may be creative, but, Henry, you had a --

DR. CLAMAN: Several comments. One, you are a cynic. All right?

No. 2, this reminds me of what goes on in Vermont on the dairy farms, where milk is sold by weight and which sometimes the weight is increased with water, which led Henry David Thoreau to say there is some

circumstantial evidence, which is very strong, such as when you find a trout in the milk.

DR. UMETSU: I just have a question regarding what happens when a lot fails because it is too high. Can you just dilute it out a little bit more?

MR. HAUCK: It all depends on your license and what you have negotiated with FDA. In general, you may have to do an investigation and if the investigation suggests that it is maybe a raw material variability possibly, then if your license permits it, yes, you can dilute it.

If it is something else, it may be your assay system is a little off. There could be something wrong with the reference. It is possible, but it is not always the case. So, it is theoretically possible, but it depends on the individual manufacturer and how their license reads.

DR. OWNBY: Are there any other general comments or discussion on this?

DR. SOTO-AGUILAR: I would like to ask a question.

In what other ways does the FDA have an input in the manufacturing process of the allergens? This is based on a comment that I heard recently, actually earlier this week, that the FDA would do actual

inspections of the plant. Is that correct or not? That is what I was told.

So, besides testing any particular lot, does the FDA go and visit the site?

MS. BRIDGEWATER: Yes. Actually, I am glad you brought that up. Yes, we do have an aggressive inspection program, as manufacturers can comment on that. But when somebody is licensed, we do go out on biennial inspections and inspect the facilities and if the CBER inspectors are on the inspection, this is also something that we would be looking for; failure rates and failure investigations are always something that are part of an inspection.

MS. LIBERA: Why wouldn't both the manufacturers and the FDA have the same system? Wouldn't that ensure the consistency and, you know, all the other things. I guess I am having a hard time understanding why you have one system for a manufacturer and then another for the FDA.

DR. OWNBY: I think Jay is going to answer that, but they are, in fact, the same system with standardized protocols. The only question is the limits on what is acceptable within that.

Is that correct, Jay?

DR. SLATER: Sure. The systems are identical

and have been identical and will continue to be identical. The problem that we are trying to escape is the problem of an extract that comes in at the edges of that curve. We have accepted that an extract at the edge of the curve, say just inside the limits is okay, we have to also acknowledge the fact that an extract that is at that okay level is so close to the border that when we test it, we have close to a 50 percent chance of failing it, even though more extensive testing, as Rich said -- if you tested it a thousand times, you would know it was .75, which is within the limits.

But you don't test it a thousand times. You test it three times or six times and that lower number of tests leads to a spread, just as throwing the dart at the target, even if you are really good, you are going to have a spread around the target.

So, it is that spread that we are trying to deal with with this. What we are doing is we are -- based on the clinical data, we are accepting that the limits could be somewhat broader than they are. We are requiring the manufacturers to do nothing to broaden it.

Remember, their licenses say they still have to aim at reference. If we have evidence that they are not aiming at reference, such as a drift downward or a failure rate greater on one end than on the other, we

have some statistical evidence that there is a problem in terms of their executing what they have said they would do in their license.

So, the manufacturers need to give us the same products they have been giving us since their licenses were approved. What we are simply acknowledging is the statistical limitations of our ability to analyze finally those products that are at the edge. If we had a perfect way of measuring those products that were at the edge, either by having a better assay or deciding that we could have our biologists do a thousand tests instead of 3 or 6 tests, then we probably wouldn't have to have this discussion because we would be able to agree with great certainty as to where it was.

We would have to figure out a way to deal rationally with the uncertainty and protocol until now, rational as it was, the idea -- they have the same limits, we have the same limits -- led to irrational results at the edge.

MS. LIBERA: I guess I am trying to figure out which patients that are on the edges that those will get that --

DR. SLATER: Right. So, the first part of the analysis then is to see whether patients would be hurt at the edge, whether patients would be injured by falling

over one side than another. There are a couple ways to approach found that there was minimal likelihood of injury at the edge, we can say, okay, we can acknowledge that there is some imperfection in our methods and broaden the CBER-imposed limits beyond what the manufacturers need to impose when they send us product.

The other approach would be, well, if we decided that the safety considerations were overwhelming, then we might say to the manufacturers, do a hundred tests. Give us a real hard number. Narrow the sigma.

DR. OWNBY: Gail.

DR. SHAPIRO: I understand the plateau in the patient response. So, I feel comfortable about the safety issue because of that. But I don't understand -- and I am no chemist and this is probably very naive, but why can't FDA provide a phantom of identity to pharmaceutical, to the manufacturers, so that they can all aim to the level that is 1?

Also then is there a problem with licensing in terms of just adding solvent or solute to get to that level? Is it like wine, where you are not supposed to fortify it or is it something where you could do it that way?

DR. SLATER: Let me answer the first question because it is easy. We do. That is the reference that

we send out. So, when we shipped nearly 2,000 vials of reference in 1999 out to the manufacturers in 104 separate shipments, that is what we were shipping them. We were shipping them the reference material that they are using as their standard and that we use as our standard. So, in fact, we are duplicating exactly what they do in our lab. That is the whole point --

DR. SHAPIRO: I think it is hard for those of us who aren't in the lab to realize there can be such a discrepancy when systems are supposed to be the same. It is sort of like stepping on the scale and having it say 150 and 170 the next day.

DR. SLATER: And there was a time when scales did exactly that. Okay? Or worse than that.

DR. SHAPIRO: I know. Obviously, that happens and it is kind of mind boggling.

DR. SLATER: When you first switch from, you know, a balanced scale to a spring scale, the old spring scales had exactly that kind of horrible accuracy and they have improved substantially.

We can anticipate improvements as well and a whole part of the presentation this morning was aiming towards types of assays that might be more precise. But we are -- you know, I don't want to convey the feeling that a competition ELISA is a rotten test. It is

actually a great test. It really works very well, but these are the limitations of the test. The sigma that we have found for the test is based on hundreds of tests that have been evaluated, initially, ten years ago and then more recently a year and a half ago.

A lot of testing has gone into this and these are the limitations of the test as it currently exists. So, we are sort of stuck with that.

DR. SHAPIRO: So, if somebody sends in a lot that is rejected because it is low, can they just spike it with more and send it back? I mean, that would seem to be a legitimate way to get to the right level. It doesn't sound like you would have to throw anything out or --

DR. SLATER: It is actually not that simple --

DR. SHAPIRO: I figured it wasn't, but it just sounds like it should be.

DR. SLATER: And the manufacturers need to submit, need to have submitted in their license applications ways of handling these kinds of materials and their SOPs, their standard operating procedures, for handling materials that have not passed lot release needed to be removed and approved. I mean, it is not trivial and it can't be done after the fact. It has to be done with the standing operating procedure in place.

DR. LEHRER: What are the ways of handling that situation.

DR. SLATER: I am sorry?

DR. LEHRER: You said the manufacturers have -- there are several ways that they can handle that situation if a lot is rejected. Gail asked if they actually can combine it with a higher potency law. You really didn't answer what ways there are to handle that.

So, I was curious to know what can they do?

DR. SLATER: Yes. I don't like to give answers that I am not exactly sure what the --

MR. HAUCK: Let me give you an example. If it is something that may have a single standard of potency, like mite, you sell 10,000 or you sell -- generally, if you are a manufacturer or -- or cat, you are selling 10,000 and that is all you are licensed for.

If your cat extract or your mite extract doesn't meet that minimal standard of potency, by and large, most manufacturers do not have a provision for doing anything with that except throwing it away.

If it is something on the other hand like a grass extract, where you are selling two potencies, a hundred thousand and 10,000, there may be a provision in your license. If when you make your 10,000, which is generally a tenfold dilution of your hundred thousand,

but nonetheless has to be tested, if it comes up a little low and you have the hundred thousand, you may just fortify with more hundred thousand and that may be permitted, depending on the individual license.

So, in most cases with the exception of possibly the grasses, there is not much you can do except throw it out for most manufacturers. Is that --

DR. PASTOR: I would like to just add one thing because it is a great opportunity to get to speak with you all this stuff, is that I just want to go back to that scale analogy one more time. The ELISA is like a scale. If you weight 100 pounds, on any given reading, you step on that darn scale, it will read between about 53 pounds to like 197 about. So, now, you say, oh, my God, that is terrible. What you do then, you step on the scale a bunch of times and take a bunch of readings and after many, it will gradually end up being like one of his readings. But because we can only take three, you get some idea, just in a way that we are dealing with something, that with three, that scale will read between 70 and 150 pounds.

So, therefore, it gives you a better sense of when the manufacturer comes in with something that is like 80 pounds and we measure it with something that really within a factor of 2, why we have this problem. I

don't want to pursue something that really sounds kind of childish, but that is the problem. The scale has a huge variability. So, it is hard to solve this problem and that is why we came up with this way of solving it. It is not an analytical method. It is physical chemistry. It is biochemistry.

DR. UMETSU: I understand the sigma and the statistical analysis of this but I still don't understand why the manufacturers do 6 in some instances, 6 determinations versus 3. It seems to me that the sigma will be reduced quite significantly by doing 6 rather than 3. If you could just sort of standardize the number of determinations, I think that might help reduce some of the variability.

DR. PASTOR: Almost all the manufacturers use sets. There are a couple that actually use 3. It was just in the process of the licenses that some of them had results that were varying over a wide range. So, we said, well, you are failing these tests, the boundaries. You guys ought to use 6. Others, maybe for just blind luck, maybe because they had been processing it really well -- we don't know -- they are licensed -- their lots and their shelf life studies are all very close, around 1.

So, we said, okay, it is just like sigma 3, but

all the large manufacturers are actually with 6. It is only some of the smaller ones that are using 3. It is just the way it played out. We don't have the -- I mean, you might argue to us -- I mean, you as a group could say, no, you should make all those other guys do 6, too. I don't know what we would do, but you could ask us to and we could find out. It is just what happened, just the history of the thing.

Is that a fair way to say what happened?

MR. LANKOW: I am Richard Lankow. I am with ALK.

I think one of the things that isn't really clear here is that we are not talking about variability of the product that comes out our pipe at all. We are just talking about the variability in the measurement method. A lot of that just has to do, are we confident in our operators in the way we do it and how tight the product is that we make. So, that kind of kind of influence the way people do it.

So, it is really looking at the measurement method and not the product. So, it is our risk. It is our risk if we or somebody else does 3 or 6 or 9 is, you know, what is the chance that when it comes to FDA and is repeated -- and, again, we are just talking about repeating the same assay on different days in a different

laboratory, what are the chances it is going to fall outside of that?

So, it really is kind of an internal operating decision that gets made and analyzed.

DR. OWNBY: Anyone else which to make any comments or an opinion on this or still discomfort with trying to make a decision? I think everyone except maybe Dan hasn't made a comment on this.

DR. EIN: Yes. I thought it was clear enough to me.

DR. OWNBY: Any other questions? I don't want to cut people off, but I get a sense that people have pretty well covered their questions and concerns about this.

I think the one thing that gives me some reassurance is the fact that this isn't the only quality control. I mean, the FDA is investigating, is checking the records, is following the source of material from the time it is originally derived all the way through this manufacturing. This is just one little bit, if you will, of a total quality program. It is not the only thing that is done to try to make sure that these are adequate products.

DR. EIN: I just want to make one comment. I think it is really instructive to go to a manufacturing

facility and see how these products are made and the kinds of controls that now exist because of tightening of the FDA processes. It is really very impressive.

I had the privilege of going about a year ago to one of the plants and it is really very high tech, high sterility, quality control, from beginning to end, which gives me -- it doesn't speak to this particular issue, but in general, following up on what Dennis said, it gives you a lot of confidence in the product.

DR. OWNBY: Okay. Well, I think we are ready to vote on this issue then.

Bill, you had a --

DR. FREAS: Before we do vote, I just want to for the purpose of the record state that there are 11 voting members sitting at the table and for the new members, I want to make sure that you are aware that you can either vote CBER expanding the lot limits. You can vote against CBER expanding the lot limits or you can abstain.

DR. OWNBY: Should we take a show of hands on this or --

DR. FREAS: That would be fine.

DR. OWNBY: A show of hands would be adequate here? Okay.

All those in favor of the proposal to expand

the limits as we have discussed, raise your hand.

DR. FREAS: Eleven.

DR. OWNBY: I take it then there are no people opposed to it or abstaining. None. Okay. That item is out of the way.

Now, these next two items, I don't think we have to have a formal vote on, but we have been asked to give our opinion, the first one being whether CBER should implement the proposed algorithm for standardization of new allergens. I think Jay adequately outlined that. The purpose of the algorithm, the other comment I have heard is that perhaps manufacturing concerns should be also included within the algorithm.

Are there other questions, comments, concerns, discussion?

DR. WRAY: My question is how different is this from what happens now? This sounds very good, but I just didn't know -- is it really different or is it just really putting in print what happens now.

DR. SLATER: Great question. It is fundamentally not terribly different from what has happened so far. It has a few differences. The exit points are different. The fact that it is formalized into an algorithm that we can sit and discuss and argue about, perhaps, I think is different as well. We wanted

to make a process that was transparent so this discussion could be -- could focus on different points.

Also, we anticipate standardizing several different products at the same time. We are going to be at different points in the process with all of them. This is simply almost an administrative way to make sure we are keeping track of the process and make sure we know where we are and where people are going.

In terms of -- does that answer your --

DR. WRAY: Yes. Thank you.

DR. SLATER: In terms of your point about getting manufacturing and manufacturers more involved, I glossed over that. In fact, on the algorithm that you have written out, on the right hand column, there are boxes for potential collaborators to be involved with us. APMA is involved in one form or another at almost every step of the process.

Again, this is a process that we are announcing in advance in this way and our intention as we move forward with the standardization of allergens is for the entire process to be transparent and as inclusionary as possible.

But, again, I don't think that is a radical difference. I think we are simply formalizing the process. If there are differences in terms of

collaborators, I think we explicitly would attempt to enlist help from NIAID, for instance, but I don't think that is a radical change either. I think that is always a possibility.

DR. CLAMAN: A small technical problem on the expanded algorithm. You have up at the top and about a third of the way down initial testing for IgE binding, assess human IgE antibody binding Western blot. Then about equal way down, you have clinical efficacy measures, skin tests, bronchial hyper reactivity, immunotherapy trials, evidence for IgE binding again.

I assume that if there was no evidence for IgE binding at the top, you would never get down to the bottom. It is a little hard to imagine having gotten down to the bottom with no evidence of IgE binding. I suppose this stuff should turn out to be negative on skin tests and people known to be sensitive, which is --

DR. SLATER: No, I quite agree. I think if there were no evidence of IgE binding on laboratory evaluation, I think we would be hard pressed to abort the process right then and there. But I think what I was trying to say is that what we are looking for in the clinical studies is not only dosing assessments of biological unitage, but looking for clinical verification that this is an IgE-driven process.

DR. CLAMAN: I have no objection at all. However, from the logistical point of view, there is an enormous difference in the time and effort required to do (a) skin test, (b) -- which take 20 minutes once you get it going -- bronchial reactivity, which is a pain in the neck and immunotherapy trials, which take years. Who is going to make these decisions as to which of these or all of these are going to be used in a given case?

DR. SLATER: Well, I think because of the reasoning that you just laid out perfectly, the default position would be to do skin testing. It would be the fastest and it clearly would be the most appropriate for most of the allergens that we would possibly be looking at. There are currently going on at NIAID in the intramural program, rush immunotherapy trials, looking at lymphocyte transformation. These are certainly not projects that are finished in an afternoon. They take eight weeks to complete, but potentially if we had a product for which skin testing was somehow for some reason either engineered or natural in inappropriate or inadequate test, we could attempt to collaborate with the investigators at NIH.

There are other possibilities as well. I think, again, this falls into the line of trying to incorporate enough vagueness into the process, so that we

had -- nonetheless that we had a process, we had a step at which we had to start making clinical relevance and dosing and unitage decisions.

We have to some method by which we are going to establish biologically-based unitage. But I didn't want the process to be boxed into a particular model, in case, as we moved along, we found allergens for which that model --

DR. CLAMAN: I agree entirely. I am a big -- in spite of the fact, I am supposed to be a scientist, I am greatly in favor of vagueness in some cases because you don't get your hands tied by your own procedural methods, which I have seen happen rather often.

DR. WRAY: There continue to be some little hints in papers suggesting that oral allergen immunotherapy works. Is there anything in the works or any interest in that? What if somebody came to you with a proposal on that? Would the same sort of standardization be required or is that just so way out that we haven't thought about that yet?

The decision as to whether oral immunotherapy works would be based on good science to demonstrate that it works. In order to have good science, we would need to have a product that was standardized somehow. It would be hard to attempt to standardize the product based

on the study verifying that the method works. So, we would need to have some independent method of verifying the potency of the product.

But the actual -- that is actually a little bit outside of what this algorithm is proposing. What you are talking about is novel methods of immunotherapy, novel delivery methods of immunotherapy. That would be more appropriate to be studied by investigational new drug applications.

DR. OWNBY: Other comments?

Yes.

DR. SOTO-AGUILAR: I would like to go back to the skin testing part, please. I don't know if I am confused on this or not, but I understand that as new antigens are being developed by the manufacturers, at the same time the FDA is interested in identifying those that have the best quality to use a reference for future use and to compare new products coming in. Is that correct? Is that something you said earlier this morning?

DR. SLATER: It is correct, except for the tense in which you said it. There currently aren't any skin testing protocols going on with -- well, if you are talking about new products, yes, if a new product came along that was under IND, very likely the sponsor would be required to do some intradermal skin testing to

establish the potency of the material.

Is that what you are asking?

DR. SOTO-AGUILAR: Right. And once you have a material that has 100,000 BAUs and you think is going to be stable and excellent product and then other manufacturers bring similar allergens and the same type of allergen, are they going to be required to be skin tested, too, all of them or only in the process of selecting reference product?

DR. SLATER: Well, if another manufacturer is coming along with a product that has the same name, but may not be identical, they would probably be required to produce skin test data with that product as well.

DR. SOTO-AGUILAR: And that applies to your algorithm. I just wondered if there was any other place in the algorithm to include the skin testing again later on?

DR. SLATER: It is not formally included in the algorithm. It certainly is a very good thought. In other words, several years later, coming back and validating that the reference material still is on target with skin testing. That would probably fall under the post approval stage. I would think that that would be a very important ongoing part of the evaluation of the reference materials as you get several changes out.

DR. SHAPIRO: Jay, I have a question about new antigens. If something were to come along, as Betty mentioned, if some developer put together an oral vaccine or a new super antigen that they felt would be excellent for immunotherapy, does the lab ever get in a position of having users come or manufacturers come to you and offer user fees to promote the standardization or the proper pushing through the algorithm faster for their particular product? Is that a possibility, if some venture group were to say we have got a new super duper vaccine and we want your group to help validate it? Does that make no sense at all?

DR. SLATER: It sounds like it takes a conference call over here.

MS. BRIDGEWATER: Are you talking about user fees --

DR. SHAPIRO: If there was a food immunotherapy issue and somebody isolated the peanut allergen. They felt that the potential was fantastic for immunization with peanut and they wanted to be the standardized allergen and have FDA approval for their product. For other divisions of the FDA, there are user fees and people can get fast tracked. Do you have anything like that? Or would it be even conceivable that you would?

MS. BRIDGEWATER: Well, first, on the issue of

user fees, once again, allergenic extracts are exempted from user fees under the law. So, they don't pay user fees. So, that would not be an issue.

Your question about fast track, it is something that somebody could come -- there is a process for coming in and trying to get fast track approval. So, they would be eligible for applying under that method, but they would not have to pay user fees.

DR. SHAPIRO: So, there is a way to bump your priorities. I mean, there might be a way to bump the priorities.

MS. BRIDGEWATER: Sure. If something comes in that is for a serious or life-threatening condition and a manufacturer can make a good argument that it is, you know, a significant public health benefit or it has indications for a serious or life-threatening condition, then, yes, there is a way to get yourself in what we call fast track approval that does push the priority up.

DR. LEHRER: I just wanted to make a comment expanding on what Gail mentioned and something that was said earlier with regard to new ways of using established allergenic extracts that haven't been approved as yet or even making available or standardizing new allergenic extracts that had not been available or not been standardized. Jay had indicated at one point that a lot

of this would be based on research that has been performed or information that has been provided, based on other studies, which I think has been fine and has served us reasonably well through the seventies and eighties, but as we went into the nineties and certainly now, I think there is really minimal funding from traditional sources for allergenic extracts. You know, such as the NIH, I think, if you want to definitely kiss a grant goodbye, put in a study of an allergenic extract.

Certainly, industry has cut back on funding of allergenic extracts as well. The FDA has very limited resources. So, I just wanted to make the point that it is something that I think everyone should think about in terms of where we are going with allergenic extracts. If we are relying on information that has been funded by traditional sources, that information isn't going to be there. It will carry you through for some of these, you know, cockroach, for example, that there has been a lot of studies up until now, but it is not going to in my opinion in the future and it is something that we will have to deal with and I think relates in part to what you raised.

DR. OWNBY: Do I have a sense of the committee concerning this particular issue of whether we should recommend acceptance of the algorithm at this point? Is

the general feeling that people are in favor of it and that we don't see any major fatal flaws or big problems with pursuing it at that point?

Okay. I think we are probably done with that. Is that sufficient then?

The last item is whether the next three items targeted for standardization should be cockroach -- and I understand from Jay that would be at least two species of cockroach, perhaps three; alternaria alternata and aspergillus fumigatus.

DR. EIN: I would like to ask Jay to expand a bit on the rational, not for the cockroach because I think there would be consensus about that, maybe aspergillus, but certainly alternaria. On what data was that decision made and why that rather than dog, for example? Is there any quantitative data about which are more important allergens in terms of asthma? So, if you can talk about that, I would appreciate it.

DR. SLATER: I think when I was asked to develop a plan in terms of responding to the asthma initiative, as you can imagine, the first choice was obvious. I think choosing cockroach was very easy. I think the idea of going after aspergillus fumigatus and alternaria, I think, was clearly less clear. I didn't feel that I could propose those two and dog.

I do think that there is some rationale for standardizing dog extracts. I think the science is there as well. I think the data are less convincing that dog is really that important, that dog allergen is actually that important in terms of the etiology of asthma.

What I was looking for were allergens that were reasonably characterized, not completely characterized and in which the relationship to bronchial hyper reactivity had been reasonably well studied, at least in some controlled situations. Cockroach, aspergillus and alternaria seemed to fit that bill.

The data are clearly the weakest for alternaria. I agree with you on that. But I think, in fact, the data on alternaria are probably pretty comparable to dog, for which the connection is weak, as well.

I am very open to suggestions about other allergens and I am open to the possibility as well -- and I would like to open the possibility that you may simply wish to expand the list.

DR. LEHRER: I must say that I was somewhat taken back by the remarks that Peter Hauck made concerning fungal allergens initially having been one that has been both intrigued and frustrated by the study of fungi as zero allergens. I think clearly I think we

all can agree that there are certainly very important, but they are very, very difficult to study.

Nevertheless, because a problem is more challenging -- I am raising the question -- should we just allow the extracts to be perhaps, you know, of less quality, at least some of them compared to others.

On the other hand, I think Peter's point was well made and that there are limited resources available for standardization of allergenic extracts. The study of fungi as allergens can be an unending task and it is not related as much to the allergens themselves, I think, as to the variability of the fungi and the production of allergens in which, you know, you see tremendous variability within the same strain, grown in the same lab by the same people.

I am still kind of struggling with this issue myself because there are other allergens, I think, that are probably equally important. For example, I think in general an area of allergy and certainly in allergenic extracts that have not been as well-characterized and, you know, people die every year of food allergic reactions and also related to the FDA's mission with regard to GM foods, we certainly need to have more information on food allergens. That would relate to that mission, although I know it is not the primary concern of

this group.

So, I am not sure. I think one thing I -- I think a good point that Peter Hauck made was that, perhaps, one should have maybe some limited objectives with the fungi. You know, as I said, there is certainly a great need to have better fungal extracts, but if it turns out that this is a much more difficult task than anticipated or requires greater resources, which could be spent better in other ways, then if you had a limited approach and if it became clear that this wasn't going to be reached, then perhaps these resources could be devoted to other allergens.

I don't know if this makes any sense or not, but I am a bit concerned about that because one could put a lot into fungi and not come out with anything.

DR. SLATER: I think the comments make a lot of sense. I think definitely the fungi are a daunting target. I guess my one response to it would be that although clearly the objective here is to come out with standardized allergen vaccines that will improve the diagnostics and therapy of fungal-induced allergic disease, I think on the way there we can actually, potentially, learn a great deal about even just in the preliminary evaluations, just learning about what the variability is of the products that are out there

currently and perhaps by enlisting the help of some of the research labs that are doing a lot more work with fungal allergens at this point, really trying to do some good, if you will, descriptive or normative studies of what is out there to draw some conclusions about what the need might be.

I think even the initial evaluation process for alternaria and aspergillus would be very instructive.

DR. LEHRER: Just to expand upon that, one point that you made early on in the discussions today was that -- I forgot exactly how you phrased it, but it was, I think, talking about techniques and using different approaches for different allergens and I think this is a perfect example in that you may not be able to use the same approaches that work so well with grass pollen allergens or other pollen allergens in which you have large amounts of relatively stable sources of allergens.

So, again, I am repeating myself, but you may want to have perhaps a little more limited approach and, hopefully, you know, what I say won't hold up, that it won't be as difficult, but if it is then you -- I think it would be a good idea to have an alternative approach so that the resources will be well spent.

DR. SAXON: Jay, last year, we actually made up a different list. The list included peanut, tree nuts

and latex. Now, I am familiar with the assessment issue. I spent all day yesterday chairing an institute session at the NIH for asthma. What has happened? It has been a year. Are we going to just throw latex away, throwing peanut away, throwing tree nut away because of this initiative?

Though I think it is important that the FDA participate in the asthma initiative, what about the other things? This is a big sea change all of the sudden, it seems to me. I wanted to know what happened in the last year to those other three antigens that were given high priority a year ago.

DR. SLATER: What happened in the last year was the effort to try to formalize the process so that we could move forward at this point. The DHHS initiative really appeared on our radar screen fairly recently in terms of coming to CBER and asking us to make a specific proposal regarding standardization in response to the asthma initiative.

No, peanuts and latex are not off the radar screen, nor are tree nuts. I think those were main valid targets. At this point, the asthma initiative has by virtue of sort of encouraging resources in one particular direction that pushed us one way versus another. They are not exclusive. We had resources before that we could

devote to standardization. So, I think that I don't intend to ignore the other potential allergen targets and certainly I think that we can move forward concurrently with other ones as well.

DR. OWNBY: Jay, I have got a question and I think through the committee is whether there is a fixed amount of resources that can be devoted to standardization or whether you think that there will be that amount and additional resources through this asthma initiative that might allow you to look at other standardization targets. That is, do we have to prioritize within a single budget or is there a chance that if we prioritize in a different direction, the budget expands?

DR. SLATER: There is a possibility for budget expansion.

DR. OWNBY: Okay.

DR. LEHRER: With the asthma initiative, are any monies being made available for the study of these allergens?

DR. SLATER: The asthma initiative is a strategic plan intended to have the member agencies within DHHS build into their budgets plans to advance the goals of the asthma initiative. So, there is no amount that was committed to the asthma initiative to start

with.

That being said, the budgets -- our budget for this fiscal year and next fiscal year are already there. So, when we first started talking about the asthma, we asked whether money could be made available before FY 2002 to support moving forward aggressively with these and the answer was "yes."

So, we potentially have additional funds that will be available effective very soon to support allergen standardization as part of this particular initiative for the next year and a half and then thereafter it will be built into the budget requests that we have been told would be supported as it went up the line.

DR. CLAMAN: I would like to support what Sam said about the difficulty with mold allergy and trying to remember whether he was the one that gave that lecture that I heard that convinced me that mold immunochemistry was a can of mold. I think it was you.

Very difficult and one wonders how much resources should be -- whether it should be done in an incremental way.

My second comment is a question, the answer to which I should very well know, but I don't. It has to do with dog allergens. Is there compelling evidence that there is a single major dog antigen, which crosses all

species and strains and, therefore, that is the one that you would put your money on, like in Fel d 1. Is Can f 1 really that predominant? Because if it is not, then you have to deal with the problem of the other possible species or strain specific antigens.

DR. SLATER: I think it has been found in all strains. I know it hasn't been found in all species.

DR. CLAMAN: I wouldn't be surprised if it was found in all strains, but is it the major allergen? That is a different question.

DR. SLATER: I don't know the answer to that.

DR. CLAMAN: I don't know either.

DR. OWNBY: It doesn't have nearly the dominance. If you take cat allergic people, you can absorb out almost 90 percent of the IgE across a pool with Fel d 1. With dog, with Can f 1, I think it is more like 30 percent. So, there are clearly a number of other allergens that have a fair amount of reactivity.

DR. CLAMAN: Which makes sense from clinical experience as well. So, there is another problem with dog there, having standardized Can f 1 and everything like that. You have only gone part way.

DR. SOTO-AGUILAR: Coming from the south, clinical experience shows that molds are extremely important allergens and we are not just talking of

aspergillus and alternaria. Alternaria is very prevalent in the south and immunotherapy results have been very efficacious actually in the patients.

However, the problem is the impurities. So, I guess it will be worthwhile doing this effort at separated dose enzymes that tend to make sure the grass is in the same extract mixture. I think that is a major problem in immunotherapy.

DR. WRAY: Do you have the data on, for example, cockroach and the relative potency as produced by the manufacturers now of the glycerinated extracts? Like, for example, with the grasses here, with the glycerinated extracts, it was really only the red top that was so way out from batch to batch. Is cockroach very variable?

DR. SLATER: Well, many of them were beyond what we would consider to be the safe limits. Only the red top was --

DR. WRAY: Only two were above 4. But what cockroach, do we have that data?

DR. SLATER: No. That is --

DR. WRAY: I just wondered how much the standardization is going to improve the extract. So, we need to know how much it varies now.

DR. SLATER: That is a perfect question. That

is the process that we haven't started yet and that is the process that we hope to begin.

DR. LEHRER: Kind of related to that, though, cockroaches and molds were identified, I think, as the two extracts that they have the highest level of proteolytic enzymes in them and, hence, the potential for degradation and also for causing problems when you mix them with other allergenic extracts. So, I think certainly any information that you gain on cockroach allergen is going to be very important.

DR. OWNBY: I think there is a consensus that the committee could easily agree on cockroach and there is a lot of concern about mold and that the other candidate would be dog. Considering that, at least in my own studies, and I think national data, there are about twice as many dogs in houses as cats, and that the analogy should hold, I would suggest that you pick one of those molds, probably aspergillus, you have better data on and use dog as your third one in terms of asthma. But I would be willing to have input of other members of the panel on that.

DR. SAXON: Again, I agree, but I just want to say we shouldn't drop the others off the radar screen because of the asthma initiative. There was strong feelings about peanut, latex, tree nuts before and those

should just be kept on the overall radar screen separate from the asthma initiative where they are not so well-known.

DR. WRAY: I think clinically we pediatricians also see foods that cause wheezing in children without necessarily full blown anaphylaxis, to make a case for foods being important also.

DR. LEHRER: It seems like what Jay was saying, though, was that there would be extra funding available through the asthma initiative for this standardization so that if that is the case, then I would be more favorably inclined to go along with the recommendation because I don't think it would bump these other allergenic extracts that we think are important to standardize. Then in a year and a half from time from this -- during this period, if the approach is not fruitful, you know, I would think that the agency would have the not to pursue it.

So, my concern was that this may take away from other -- from standardization of other allergens. You are telling me that this will not.

DR. SLATER: The entire effort at putting together the algorithm for going forward with standardization originated long before I was personally aware of the asthma initiative at all. The people that

were involved in developing the consensus and developing the algorithm, most of that went forward before we were asked to make a proposal for the asthma initiative. That is -- the idea of going forward with standardization, with picking rational targets, with moving forward aggressively to try to standardize new target allergens, such as peanut, was in the works before the asthma initiative came on board.

Andy, I don't really think the asthma initiative has co-opted the process at all and the way that we phrased the question is we phrased the question -- if you look at the second part, it says "Given the support of the asthma initiative, we would like you to assume that the added money is there to support this." And, therefore, what we are looking for is your guidance, assuming there is money to support the asthma initiative in our activities.

Then, are these reasonable choices?

DR. CLAMAN: I think that the situation is complex. I don't want to find myself in the position of telling a good scientist what to do. Besides, it doesn't work. He has, I think, heard our concerns. We meet now and then. He works with us on a daily basis. I think he knows what funding is available. He knows the complexity of the system. He lives with it everyday. I think we

trust his judgment to do what seems to be best to do.

MR. LANDOW: Since you are close to having a consensus, let me throw one more thing in without making a commitment either way just to think about from a strategic point of view. Are the things that you propose to standardize going to have a big impact in a lot of ways? I mean, as a manufacturing company, as we go through our strategic planning, we have to ask questions that a number of you have touched on before. How many people get treated? Is it a treatment?

You talked earlier -- is it an immunotherapy product? Is it a diagnostic product? The market for diagnostics is that big. The market for immunotherapy is a little bigger. It is not big. This entire industry we have is less than three weeks of Clariton marketing. So, you know, there are some issues.

When we look from a strategic point of view, we look at the treatment or the options that you as allergists have with your patients, avoidance, pharmacotherapy, immunotherapy. If you can avoid it, avoid it. So, again, that -- I am not sure what I am saying. I just know that we are discussing a lot of these same kinds of issues and there are a lot of impacts and you have a real challenge in deciding how to have really good scientists spread themselves over more

objectives than they have time for.

DR. OWNBY: I was just wondering from the industry's perspective, since you know your marketing numbers much better than we do, is there some other extract that would have a major impact on the health or at least from your idea of sales that we haven't been discussing here?

MR. HAUCK: I believe in the past we had given out some marketing information to FDA, but I think as an organization, since we are meeting at the academy meeting, maybe we will raise that among our membership and provide some guidance because that has probably changed. The last time they asked for it, I think, No. 1 was house dust.

DR. OWNBY: Okay. Are there any other -- is that an adequate answer in consensus from -- okay. Are there other items or other questions that need to be brought up today?

Bill, did you have any concluding remarks or items that we need to cover?

DR. FREAS: That is it. I just want to thank you on behalf of FDA. We truly appreciate all the committee members coming across country and from around the area to give us your suggestions, comments and recommendations. These are very important to us and we

will give serious consideration to everything.

In the meantime, I will update you on the -- I believe we have a tentatively scheduled meeting for October 24, but it is too far in advance for me to give you anything definite on that meeting. I will be updating you within a couple of months. I just thank our chair and thank all of you for all your recommendations.

Thank you.

DR. OWNBY: Thank you all for coming.

We are adjourned.

[Whereupon, at 2:20 p.m., the meeting was concluded.]