is given in your handout. Thank you very much.

DR. LEHRER: Thank you, Dr. Slater. Are there any questions by the committee of Dr. Slater's presentation? Okay, thank you very much. Now, I'd like Bill to update the committee with any requests to speak at today's open hearing, public session. Have you received any requests at all?

DR. FREAS: Mr. Dr. Lehrer, and for the new committee members, let me explain, we have this open public hearing and especially for the audience as well, so that any member of the public can address the committee on any issues that are relevant to the meeting topics and not only do we give them the opportunity, we encourage any comments to the committee. So at this time, I would have to say that in response to the announcement in the Federal Register notice, we have not received any requests but is there anyone in the audience who would like to address the committee at this time?

Seeing none, Dr. Lehrer, I bring the open hearing to a close and turn the microphone over to you.

DR. LEHRER: Thank you, Bill. Well, we are scheduled for lunch but I think it's a bit early, so I suggest we just continue with the program and

then we can see where the time is as to where we'll take our break for lunch. So the next section is going to deal with regulatory topics.

First, Dr. Slater will present considerations for the regulation of recombinant allergens for diagnosis and treatment of allergic disease. Dr. Slater?

DR. SLATER: Thank you. Let me just explain a little bit. The next two presentations, this one about recombinant allergens, what needs to come next and the discussion of glycerol in allergenic extracts are really based on our interest in having the committee be focused in these issues which we are anticipating are going to come up in the future. These are not driven by any specific regulatory questions. In fact, there are no questions associated with this, but this is a committee that we anticipate will be dealing with recombinant allergens and this is a committee that will be dealing with glycerol.

And these are not topics that have been treated in recent times before this committee and I wanted to start this discussion with the committee anticipating that we're going to be dealing with these issues as time goes forward. And I think before I even get to recombinant allergens what needs to come

next, I think it's important to sort of set the stage by talking about in broad terms, where we are with natural allergens, which is what we're actually using and have been using for quite a long time.

These are all natural products. They're mixes based largely on a completely unselective extraction of source materials. They are products that are manufactured and sold in different diluents. They are of varying potency and stability but they are a documented efficacy in the immunotherapy of allergic diseases, especially due to hymenoptera, ragweed, grass, cat and dust mite allergy exposure.

More on where we are with natural allergens, the unitage for non-standardized product is largely uninformative as to the potency. That's an important concept to fix in mind and I know I don't have to convince anyone on this committee of that fact. But standardized products are controlled for potency and stability and the standardization is based on identity to a US standard for the most part.

Standardized products still constitute only a small minority of product number, 19 products out of a universe of hundreds of products, that it's likely that they represent a greater percentage of products volume that's actually purchased and used.

We don't really have any specific data on that. Where are we with natural allergens?

Well, it's not that allergenicity equals immunogenicity which equal potency, but with natural allergens they tend to go together. If you have a more potent product, it's going to be more allergenic and that's sort of the basis of the say we standardize these products and we have really depended on this relative equivalence of these three important features of the natural products.

Products may be used for diagnosis and immunotherapy, although it's important to note that not all of them are approved for both diagnosis and immunotherapy. And there are production issues associated with certain of these natural products. As an example, you've heard a great deal about precipitates. So in summary, we have with natural allergens a diverse group of products, many of which are of uncertain potency but several of which are standardized and are of documented efficacy, both for the diagnosis and treatment of allergic diseases. This is where we are.

Where could we be? Where could we go? How could we improve the situation with natural allergens? Well, obviously, the first answer from me

is going to be we could increase the number of standardized products. The more standardized products we have the more we'll have a unitage that's actually biologically meaningful and helpful for our physicians and patients.

We can also potentially improve the standardization of some current products by improving the definition of the measured allergens. We could increase our purity standards, we could attempt to institute selective extraction techniques, purification methods and we could improve our characterization methods of these natural products. We could also attempt to improve stability, either by having more products in glycerol, lyophilizing products or perhaps other methods that we haven't thought about yet.

We could attempt to improve delivery systems. We, as physicians, could attempt to have a better definition of the indications for the use of these products and certainly as physicians, we could have more consistent and rational applications. These are all ways that we could improve the products that we currently have.

But certainly over the past many years, the promise of recombinant allergens has been raised

often and loudly and it's certainly an exciting possibility. So where are we with recombinant allergens? Well, at the moment we have in recombinant allergens extraordinarily potent research tools. And this has been demonstrated worldwide using many different allergens. These are remarkably potent tools for dissecting immune responses, for modifying immune responses in the laboratory, for looking in ways that we really couldn't look at before at allergen structure, for determining structure function relationships and for generating novel and interesting products in the laboratory.

Where can we be with recombinant allergens? Well, there are lots of opportunities. Unfortunately, the opportunities are both positive and negative and so we have to be a little bit careful but I'm going to start with the positive first. One of the most exciting possibilities of recombinant allergens is that they can be used as standardization tools. This would be a remarkably good tool for standardizing the allergens that we currently have with certain limitations that I'll talk about next.

We have the clinical opportunity to effect a real divorce between allergenicity and immunogenicity. And this is obviously of great

clinical interest and of great clinical importance. We could potentially have greater purity and consistency of product than we have now. We could have greater product stability, both due to purity and potentially due to engineering. We could engineer into the products ways to make them more stable than they are now. It would certainly be very attractive for my laboratory to have a 25-year standard product. That would be really quite attractive.

And we could potentially improve delivery systems in ways not possible using native proteins. That being said, there are also negative clinical opportunities, and I think the first two really is we have to confront the fact that recombinant allergens post a challenge to standardization in a couple of different ways, at least a couple of different ways that I can think of.

The first way is that these are really unique products with different biological features. I can now standardize every ragweed product on the market with a single US Reference Standard. There's every reason to believe that if we have multiple recombinant ragweed products, we're not going to be able to standardize them with a single US Reference Standard because they're going to have different

biological properties that are going to make it impossible to compare them to the same standard.

That's potentially a very good thing, but we're going to have to confront the fact that we're going to have to think about standardization in a very different way with these recombinant products because they are all potentially going to be unique products. It's also a challenge to standardization for the very obvious reason that we currently take advantage of the fact that the potency is really related to skin testing and there's every reason to believe that when these recombinant products come down the pike we're not going to have that relationship or we're going to have to look at new and appropriate ways to standardize each and every one of these products.

In addition, one of the things we're going to have to be careful about with recombinant products is that the indications are going to be likely to be more specific than the indications for the native products. It's extremely likely that immunotherapy products are going to be ineffective for the diagnosis of allergic disease. It's possible that diagnostic products may be ineffective for the immunotherapy of allergic disease and the usage of these products may be much more population specific than it is now.

It's not clear that if you have a recombinant product for a single important dust mite allergen you're going to be able to use it in the same population. Physicians are going to have to get used to refining the usage, the population specificity of its usage in a more defined manner.

This is an effort to outline what the process is for getting a great idea to the market. You want to start with lab-based science. You have to have some clinical interest, and of course, some financial interest in the product. You have to advance the pre-clinical safety and efficacy studies. You have to get into human studies which we'll talk about more in a couple of moments. And then finally, hopefully licensing and then as Dr. Walker mentioned early this morning, our relationship with products doesn't end with licensing. There's a long post-licensing relationship that continues on and on.

And so now we're going to get more into sort of the guts of the FDA process and how these things can actually move forward and I think it's important to review, especially for the new members of the committee, how does the FDA decide what it's going to do. The FDA owes its existence to the Food, Drug and Cosmetics Act of 1938 or the FD&C Act. It was

revised substantially in 1997.

In addition, biological products are effected by the Public Service Health Act of 1944 or the PHS Act. These are the laws that really form the basis of the FDA's existence and its activities in what it does. The laws are very specific. They tell us a lot of what we're supposed to do and what manufacturers are supposed to do but it doesn't tell us everything and the rest of the details are taken up by the regulations which is the Code of Federal Regulations which is revised regularly and in addition, there are documents that are -- that also instruct how the FDA does what it does and reflects current thinking of the FDA. These are the guidance documents and also the International Conference on Harmonization or ICH documents are products of international collaboration which the FDA is a signatory and these also give the details on how we do what we do and how we decide what we decide.

Now, what are the guidance documents that apply to allergenic products? And these can all be found on the CBER website under guidance documents. The one that I have bolded here is probably the most important one and all the manufacturers are well familiar with it. This is a "Guidance for Industry On

the Content and Format of the Chemistry, Manufacturing and Controls Information and Establishment Description Information for an Allergenic Extract or Allergen Patch Test". This was issued in 1999.

In addition, there are some guidances on testing limits for the stability of standardized grasses and the potency limits for standardized dust mites and grasses, a revised protocol. There are also guidance documents that apply specifically to recombinant products and these are listed in your handout as well. Two of these are ICH documents, two of them are FDA documents and these are the documents that reflect, again, the thinking of the FDA and the way we're going to proceed with regulating these products that are described.

So how do we get there, which is to have a product, from where we are now? We have to start by making a product that's safe and effective, that's the baseline with which we all start and certainly we have to have a product that can be manufactured consistently. The product has to be manufactured using current good manufacturing practices, these are practices that insure that the products are manufactured in a certain way that will, again, assure the safety of the product. And of course, the

necessary studies to demonstrate safety and efficacy need to be performed.

The first step would be pre-clinical studies. These are going to be product specific, looking at efficacy and mechanism. The choice of a model here is important and in addition, there needs to be toxicology studies. These are animal based studies for the product in question.

And then when you're going to get to human work, which obviously, you need to do before you're going to get a licensed product, you need to do an IND or Investigational New Drug Submission. The objective of this is to show that the product is safe and effective and it's ultimately also to support the labeled indications and the dosing of the product.

What is this IND process? This is an important process. It's based on Section 505 of the FD&C Act and Section 262 of the PHS Act and there's a fair amount of information on the website at -- on the CBER website at this web address.

The FDA's objectives in reviewing an IND is really first and foremost to assure the safety and the rights of study subjects and in Phase 2 and 3 studies, to help assure that the quality of the scientific evaluation of the drugs is adequate to

permit an evaluation of the drug's effectiveness and safety. In other words, in Phase 2 and 3 we're also concerned in addition to safety and rights of the subjects with making sure that we have a scientifically valid study that will come out with scientifically useful results.

Let's just go through the process very briefly here. Phase 1 studies is the first introduction of the product into humans. These tend to be small studies. We're looking for dose ranging. We want to get an idea of what doses can be tolerated and what might be effective. These are very closely monitored studies looking at both safety and activity of the drug in question. When you submit an IND application for Phase 1 study, you might get put on clinical hold and what would be the reason that the FDA would put you on clinical hold, that's basically our way of saying you can't go forward with the study, clearly if there was an unreasonable or significant risk of illness or injury that would be a major reason.

If the clinical investigator is found to be not qualified to perform the study, if the investigator's brochure is misleading, erroneous or materially incomplete, or if the application simply

doesn't have enough information in it to assess the risk, that would be a reason to put the Phase 1 study on hold.

And the Phase 2 studies are larger. Again, they're still relatively small numbers, hundreds of individuals. These are controlled clinical trials looking preliminarily at the effectiveness of the drug and they're pretty closely monitored. Again, we're still very concerned about safety issues and the small numbers are a way of keeping as close a handle on that.

Phase 3 studies are larger, hundreds to thousands of individuals. This is really the pivotal study to look at efficacy. Obviously, the controls are very important in this study. Now, what would be the reasons to put a Phase 2 or 3 study on hold? Well, all of the reasons for the Phase 1 study apply; risk, investigator not qualified, brochure is misleading, or just you know, insufficient information to assess the risk. But then the additional reason to put a Phase 2 or 3 study on hold is if the protocol or plan is deficient in design to meet the stated objectives. We want to make sure that you're able to meet the objectives of the study.

So this is my chance to put in a small

pitch to a captive audience for the IND process. The IND process has come under criticism on several levels but the bottom line is the IND process is extremely important. It's important for the scientists and it's important most of all for the study subjects. It really protects human subjects. It protects their safety and in a very real way it protects their civil rights.

It also improves the science by imposing a rigorous study design. It's really -- scientists should see this as an opportunity to have a number of people really pick over the protocol and make sure that the study design really is going to bring about what the -- is going to answer the questions that it has posed.

In addition, the IND process facilitates product approval because the design of the study has already been previewed by us. So it can certainly facilitate going through the licensing process.

Well, how to get there from here, what are the general hurdles for new allergens? For any new allergen, you're going to have to have some biological justification for the product. In other words, the product has to work somehow, has to help somehow. You have to have control of your manufacturing practices,

to impose good lot to lot consistency and I one of the more interesting things of consequences of standardization of allergens is really we're able to accumulate data that we published two years ago it really indicated that for grass and dust mite extracts, the manufacturers really have very consistent manufacturing practices. That's extremely reassuring and certainly any product to move forward is going to have to have good lot to lot consistency.

You have to have a good potency assay for the product. If you can't measure it, you're not going to be able to study it. And the study is going to have to be adequately powered which means you're going to have to have enough people in the study, adequate size, to support the stated study objectives.

We have reproduced here the ICH document called "Statistical Principles for Clinical Trials", which is also available on the website that really goes through in very nice detail and not into laborious and lengthy fashion what the basic principles are that we follow in terms of determining study power. Of course, one statement that's very important to make that again, I know all of you are very familiar with is that the failure to demonstrate a difference is not sufficient to demonstrate

equivalence.

And if you're looking to demonstrate the new product is equivalent to the old product, you have to power it adequately so that you could see a difference if there were one. Now, there are specific hurdles for new recombinant allergens. The hurdles that I have been talking about before are hurdles for any products but there are specific hurdles for new recombinant allergens that are dealt with in the ICH and guidance documents on recombinant products that I eluded to before.

First of all, you have to really make sure you know the character and the stability of the gene construct. And it a cell line is used, the cell line needs to be extensively tested for the absence of adventitious agents such as retroviruses, EBV or SV40. The fermentation, growth media and growth conditions have to be worked out and standardized. The purification technique has to be worked out and standardized and the final product has to be characterized. You have to know what the product is and there has to be some proof of structure of the final product.

So we need to have a gene construct that's stable and that we know what it is and we have to come

out with a product that we really know what it is and we have it well characterized.

There are more specific hurdles for new recombinant allergens. The study design must target the appropriate patient population. This may be different from the natural counterpart. And in addition, the indications for the product have to be carefully considered prior to the study design, again, the indications may be different from the native counterpart and these have to be thought through in advance.

Now, let's get to unitage. The unitage will have to be biological unless purity is assured, correlation of the biological activity to mass units is constant and the stability of the biological activity is assured under conditions under which the product will be shipped, stored and used. In other words, if we're going to use mass units for these new products, we have to make sure through adequate studies, that the relationship between the biological activity of the product and the mass unitage is going to be assured and constant under expected conditions.

This sounds like a lot but it actually has been done before. This is a list that I generated based on really not very much time looking for

recombinant product that have been approved, that are on the market. There's been quite a bit -- as you all know, there have been many recombinant products that have been derived and it certainly is something that is achievable and is doable for recombinant allergens as well.

Now, once again, I've put together a slide that must be too complicated for this but the next slide really basically just shows a number of resources that are available. It will come up eventually. There's a website on the last slide. The Academy of Allergy has a future initiatives project which -- ah, there we go. The Academy of Allergy has a future immunomodulation initiative that they are eager, they tell me, to talk to individuals both in academia and in manufacturing that are interested in developing new products.

I'm not sure what resources they have committed to this but they certainly are eager to help out in whatever way they can. The FDA/CBER website discussing INDs has a lot of information and finally, a pre-IND meeting is a resource that really can be very helpful. In fact, we strongly encourage people before they submit an IND to pull together as much information from their IND application and send it in

requesting a pre-IND meeting. This is really an opportunity to have the people that are going to be reviewing the IND go over it carefully, sit down either face to face or in a tele-conference and really go through it step by step and what is adequate, what is not adequate, what you need to do to have a successful application.

It can be done, it will be done but there are processes that have to be gone through to get there. Thank you very much.

DR. LEHRER: Thank you, Dr. Slater. I have a question. With some of the new recombinant allergens that are being developed and altered to reduce their reactivity with IgE and theoretically, make them safer molecules for treatment, have you any specific thoughts in terms of how these might be measured or standardized?

DR. SLATER: Wes. I think that's a good point. I think that the biological activity they are interested in for these would be their ability to bring about immunomodulatory changes ultimately in humans. There are models that can be developed for their interaction with target cells. There are animal models that can be developed but they do pose a challenge and in fact, what would be, you know, very

nice, would be if we could develop in the studies a really clear correlation between some easily measured unitage and the biological activity in the studies.

It's hard to imagine a lot release assay that involved checking to see how it worked in an immunotherapy model. But, you know, ultimately if these products were going to be used for immunotherapy, we have to make sure that whatever unitage we have is correlated to their effectiveness as immunotherapeutic agents. It could be mass unitage. I think that would be something that we would all welcome if the studies verify that. But there are other units that can be used as well and they might involve animal testing or testing of cell lines.

DR. LEHRER: I would imagine also that because the claim is made for a lack of IgE reactivity, that one might have to also assess for that as well, and express it.

DR. SLATER: Absolutely and that's a concern, obviously, with the stability of the construct. If the product is demonstrated to have a low IgE reactivity, we want to make sure that as its passage, it's not going to revert back to the native state and with simple mutations, that's certainly a concern.

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

DR. BURKS: The process you describe for recombinant allergens, other things that are going on that might modulate the immunoresponse from an allergenic standpoint or peptides or conjugated either recombinant or conjugated native proteins, is the same process go through for both those other types of peptides and conjugated proteins?

DR. SLATER: Yeah, I think it's basically the same process. I think, obviously my statement at the very beginning that these are all biologically unique products applies here and this really isn't meant to be a framework into which everything else has to fit. This is a framework that sort of taking the lowest common denominator approach. But as products come up there will be specific concerns about them.

You mentioned conjugates, the stability of the conjugate, the nature of the conjugate, the characterization of the conjugate, the dependence of biological activity on small variations that might occur down the line, and manufacturing consistency, that's going to be a major concern as well.

DR. LEHRER: Dr. MacDonald?

DR. MacDONALD: Yes, just a point of

information; obviously, Phase 1 needs to be completed before Phase 2 but often times in the literature you see Phase 2/3 or a company will say, "We are conducted Phase 2/3 trials". Does that mean that Number 3 does not have to be -- Number 2 does not have to be completed before Phase 3 begins?

DR. SLATER: I think what they do is they sort of fold the two applications in together and they'll have a Phase 2 section that will be smaller and tighter and then leading directly into a Phase 3 but you know, I haven't had that much experience with them but the limited experience I've had is to sort of had a chance to review the early data before they proceed with the larger study.

DR. MacDONALD: Thanks.

DR. LEHRER: Yes.

DR. SOTO-AGUILAR: I have a question. Do you have already production Phase 1 that you're studying with the idea of progression to Phase 2 in the recent -- in the short term future or not?

DR. SLATER: I actually can't comment products that might or might not be in the pipeline.

DR. SOTO-AGUILAR: Okay, well, this is the reason I'm asking. In your list of the products that already been using clinical management, I recognize

three immunomodulatory agents that are using in rheumatology, okay? Well, they are shown to be effective in the management of rheumatoid arthritis, three of these. However, what are we seeing now is that those patients some of them are at risk for developing auto immune antibodies that were never thought of before.

There's a possibility that the immunomodulation of certain diseases can lead to the development of other responses, immune responses that are not expected and that may not be surveilled or you know, monitored at this time because they have never been expected. So my recommendation or suggestion was if you are working already in some products that will be recombinant, could you assure that those individuals that are going to be tested or treated with can be sufficiently monitored before or during -- and during the process on a periodical basis for all types of auto immune antibodies that we already know so that then you can see, is there going to be a likelihood of developing some other antibodies later on.

DR. SLATER: Well, in the design of the studies, one of their very important components are inclusion and exclusion criteria and safety

monitoring. These are very important parts of these studies and the sponsors of the studies have to put into effect fairly stringent monitoring measures to assure that optimally that there will be no adverse effects but certainly if there are adverse effects, that we know about them as soon as possible and that there are stopping rules in effect to stop studies if there is an unacceptably large number of adverse effects.

I think if you want to call our attention to and sort of have us incorporate that into the requirements, I think it would be helpful if you sent us, meaning me, the information on these adverse effects and your concerns and we can certainly build them in. In addition, of course, any adverse effects that you've observed with a licensed product of any sort, via the Med Watch system so that it can be investigated carefully. But that's important information that we need to know.

DR. SOTO-AGUILAR: Yeah, will this test be future initiative for immunomodulatory agents? Also the committee of auto immunity and I'm sort of in charge of this topic and I thought it's good the FDA meeting is coming because I'm not certain that those particular findings were even expected initially.

Now those patients are more likely to be tested because they have connective tissue diseases but what if your tests your trying -- or treating patients with hypersensitivity disorders, we're talking of allergy working with the Ying and Yang of the TH1 and the TH2 paradigm and that's the main concern. So it would be nice if that could be considered for everybody just across the board.

DR. SLATER: I think you're raising a very good point.

DR. LEHRER: Yes, I think you raise a good point. Are there any other questions or comments from the audience? Now, Bill, have there been any requests to speak at the open hearing?

DR. FREAS: I believe we still have one more topic from Dr. Slater.

DR. LEHRER: Yes, I'm sorry. I'm ahead, forgive me. I apologize, Jay. The next topic will be Glycerol and Allergen Extracts. Dr. Slater?

DR. SLATER: This is the last presentation in the open session and this will not be a very lengthy one. I really, again, wanted to introduce this discussion of glycerol and allergen extracts largely because the issue came up last year in terms of precipitates and there was some interaction with

physicians and scientists as to the basis of glycerol's activity.

Glycerol is a fairly simple molecule. This is the structure of it. It's a three carbon chain with hydroxyl groups. It comes under several different names. Glycerol is the one that I prefer. Glycerin is probably the most common one that's used spelled without or with an E; one, two-three propane trial and trihydroxy propane are also names that are used in somewhat more obscure publications.

This is a widely used product. This is present in more products than you're aware, certainly many more products than allergen extracts. It's a widely used solvent; humectant, plasticizer, emollients, sweetener. It's used to add flexibility to plastic products. It's used in the manufacture of nitroglycerol, otherwise known as nitroglycerin, cosmetics, liquid soaps, inks, lubricants, glues, cements, antifreezes and hydraulic systems. This is really a ubiquitous product in industrial society.

In the allergen world, it's also a fairly ubiquitous product. This is a list of the standardize allergen products and I'm sorry, this is a little hard to read. The first column are the numbers of products that are aqueous. The middel column is the number of

products that are packaged in 50 percent glycerin and the last column is lyophilized products and what you can see here is what I eluded to before, that among the dust mite and grass pollen extracts, all of them are packaged in 50 percent glycerin.

Short ragweed and ragweed mixes most are in 50 percent glycerin but there are a fair number that are aqueous as well. Cat hair is a mix of all three formulations as is cat pelt and the hymenoptera venom and venom extracts are all lyophiled.

Why is glycerol added to so many allergen extracts? Well, probably the major reason is that it's a remarkably effective protein stabilizer. There's also evidence that it's a protease inhibitor and finally there's some evidence that it's bacteriostatic.

How does it stabilize proteins? My guess is that the major way that glycerol stabilizes proteins is by freezing point depression. When you have 50 percent glycerol, it will not freeze even if you put it in the freezer. And as you know, freeze/thaw cycles are quite effective at denaturing most proteins and so depressing the freezing point my guess is one of the major ways in which glycerol stabilizes protein.

But that's only on the low end. It also turns out it stabilizes proteins on the high end and it's clear from the biophysicists that glycerol induces a number of confirmational alterations in proteins, causing preferential hydration, domain interface changes, reduction of the backbone mobility of the proteins and it also changes association constants of the proteins with each other and may, thereby, reduce interactions that lead to the denaturation of the proteins.

There's a wealth of literature that I'm not going to take you through in agonizing detail on the effects of glycerin or glycerol on the stability of allergens. This particular study from 1992 looks at Prosopsis Juliflora pollen or mesquite pollen, Rhizopus and wheat dust. The problem with these studies is that they all use different unitage and different ways of expressing it. This particular one is looking at percent reduction of RAST inhibition of the three allergens at 40 days of storage at various temperatures.

So this is reduction of RAST inhibitions, so zero means it's the same potency as it was to start with and you can see here on the left panel, these are all in 50 percent glycerol. The right panel is the

aqueous solutions. The temperatures go from four degrees up through 55 degrees and what you can see is that at four degrees there's some preservation of the pollen extract of the Prosopsis pollen extract potency relative to aqueous but the most dramatic effect for the Prosopsis pollen is from 30 degrees and above.

At 30 degrees, which is sort of warm room temperature, in 50 percent glycerol for 40 days there was no measured loss of activity, whereas in the aqueous solution there was 80 percent loss of activity and I actually find this rather remarkable and almost unbelievable that at 55 degrees, for 40 days, the product only lost 40 percent of activity, compared to 80 percent of activity.

For Rhizopus the data are largely the same, again not much of an effect, no measurable effect at four degrees but a dramatic effect at higher temperatures, and wheat dust the effect is substantially less impressive and probably non-existent and that may have to do with the method that they use for measuring allergen content of wheat dust may simply not have been looking at anything that they wanted to measure.

Again, another study, this one from earlier, from 1982, from Laboratory of Allergen

Products at CBER, again looking at the temperature effects of -- temperature and diluent effects on the stability of the grass pollen extract by RAST inhibition assay. In this case, this is just the RAST inhibition, not percent reduction RAST inhibition, so the higher the column, the better and if you'll look here, this is a comparison of Cocas solution versus 50 percent glycerol. This is the days going out to three months and what you can see here again is that at four degrees with this particular extract, there is a reasonably good preservation both in Cocas solution and in 50 percent glycerol of allergenic activity.

When you go to 22 degrees, you see that the allergenic activity drops off somewhat in Cocas solution and is completely preserved in glycerol after three months but then at 35 degrees there's a very rapid and sustained loss of activity in the aqueous solution and a rather impressive preservation of activity in 50 percent glycerol.

And then finally a study from even earlier from 1974 looking specifically at Antigen E content and again, I'm sorry the unitage in this one is even more different. This is months that elapsed until there was a 50 percent loss of activity and again, what you can see here is that if you compare the

saline and the 50 percent glycerol saline, that at four degrees there was an eight-month interval before 50 percent of Antigen E activity was lost whereas this was a 15-month study, at 15 months, there was still greater than 50 percent activity.

This is a little bit of a hard study to interpret because we really don't know whether, you know, this was 50 percent and this was 55 percent. It's a little hard to know from these data as was represented here, but you can see that there's a definite trend of improvement in glycerol.

The stability of glycerated extracts is so well accepted that it's actually enshrined in the regulations in a form. The expiry dating of standardized extracts is based on real time stability studies and we have standardized extracts that manufacturers actually have to do real time stability studies to justify the expiration date that they put on the product. But expiry dating on unstandardized extracts can't be based on real time stability studies because there's nothing to measure. There's on potency measure.

So the expiry dating of unstandardized extracts is actually specified in the CFR in 610.53, and the major discriminating factor is whether it

contains 50 percent glycerol or more or it doesn't. If the product contains less than 50 percent glycerol, the paradigm that's described in the CFR is what we call 18 in/18 out. In other words, the manufacturer from the date of manufacture, has 18 months in which they can keep the product in house in their control. After they ship it, they can tag on another 18 months, so the actual stability dating of the product from manufacture to expiry depends on when the stuff is actually shipped.

If it's shipped at the date of manufacture, then it's an 18-month expiry date but if they keep it under their control conditions for 18 months, and then they ship it, it actually has a 36-month expiry date.

Now, we get to show you the cartoon a second time; with 50 percent glycerol or better, the paradigm is absolutely identical except that it's 36 in/36 out. So the dating from date of manufacture is going to be somewhere between 36 months and 72 months, or six years depending on when it's actually shipped after manufacture.

We have pretty good evidence that glycerol inhibits particulate formation in allergen extracts. This is something we eluded to before. It's an

observation that the manufacturers have made and we've made as well. In one series of observations, particulates appeared in 95 percent of aqueous extracts but only in 50 percent of glycerin aided extracts and probably even more significant, the particulates in the glycerin aided extracts in the series were significantly smaller and sometimes were actually quite hard to see, whereas the ones in the aqueous extracts were the kinds you could see from far away.

Glycerol is a preservative. There is significant amount of old data that indicates this and again, in the CFR, it's stated quite clearly that "Products in multiple dose containers need to contain a preservative except that a preservative need not be added to an allergenic product in 50 percent or more volume in volume". So, in the CFR it's specifically stated that multiple dose containers have to contain preservatives except allergenic extracts that are packaged in 50 percent glycerol don't need to.

So these are the good things about glycerol. What are the bad things about glycerol? Well, the major problem with glycerol is pain on injection and this is an observation that's been made over and over again in many contexts and everybody has

had this experience in their clinical practice. We all know this. The paper that's quoted most frequently is a study from the Hopkins group that was published in the JACI and they basically showed that the pain was related to the glycerin dose.

It's not really related to the volume of the injection but to the actual calculated dose of glycerin in that injection. And I'll just take you through that very quickly. This is basically a series of 12 different dose groups. Each dose group had 15 patients in it. It's a little bit confusing how they represented that data, so I'm just going to walk you through it a bit.

So ignore the numbers that are written next to the dots those of you that are up close enough to see the numbers. The closed dots reflect so-called Grade 3 pain and the open dots reflect Grade 4 pain which was characterized as severe pain on injection. And what you can see here is that when you have a total dose of glycerin that's less -- that's at .15 or less, almost nobody had severe pain. But when you get up to doses of .2 or greater, you had two patients out of 15 in one group and two patients out of 15 in another group who complained of severe pain.

This is the kind of pain that would stop

people from having immunotherapy, so this is the pain that we really want to be very concerned about. We also want to be concerned about Grade 3 pain, which while it doesn't stop you from immunotherapy, it's still pretty significant and may interfere with treatment and in that situation, the pain really starts earlier at doses as low as .05 mls of glycerin. So pain is really the drawback. It's really very good for the allergens but if you inject too much of it, it can be a serious problem.

The other negative is induration, so-called glycerin button was observed in a couple of studies and it was suggested that there was some increased bruising associated with glycerin as well.

So in summary, this is a very brief presentation, glycerol stabilizes allergens, especially at sub-optimal temperatures, both in the low end and at the high end. It may inhibit proteases. I didn't show much data on that because there really aren't much data of that. But as you know, proteases are an important consideration, especially with mixes of allergen extracts that are used clinically. It inhibits bacterial growth. It inhibits precipitate formation and the only real drawback is pain on injection which can interfere with

clinical treatment. Thank you.

DR. LEHRER: Thank you very much, Dr. Slater. I have one quick question. I always thought the 50 percent glycerin was used and I saw you refer to 50 percent but when I spoke to someone in the industry recently, they said that the requirement is 52.5 percent and this apparently is much more effective in enhancing stability. Could you comment on that?

DR. SLATER: No, I can't.

DR. LEHRER: Okay.

MR. HAUCK: I think that's a misperception. It's -- the regulation is 50 percent for an extract to be glycerinated or to contain 50 percent glycerin, it must have between 50 and 55 percent glycerin by assay. So the manufacturers target 52, 53 percent to assure they have at least 50 percent glycerin because there's not a whole lot of data below 50 percent.

DR. LEHRER: Thank you. Yes, Dr. Nelson?

DR. NELSON: Yeah, I think Jay presented the -- a nice balance between the advantages and the disadvantages. My concern is as a practicing allergist and one who backed off from glycerin 30 years ago, because of unaccpetability on the part of

the patients is that other people with less clinical orientation are going to look at the advantages and start pushing towards more and more glycerin. And about 20 percent glycerin in our experience, was the top that you could get away with. So right now, we can incorporate the glycerinated extracts and still stay at 20 percent, but if more and more are pushed to glycerin, then we're going to be in a bind.

It seems to me that the lyophilized extracts have all the advantages of glycerin and also get away from the precipitate problem and I wonder if there's any intent on the regulatory people to start pushing the manufacturers towards lyophilization rather than towards glycerin.

DR. SLATER: We are certainly -- I'm certainly sensitive to the issue of pain on injection and to the degree that I might have been a little insensitive at a meeting at the Academy last year, I was clearly put on notice that it was a major issue for clinicians.

Our concern is the safety and efficacy of the products and you know, we're certainly interested in anything that will enhance the stability and the reliability of the product. We're concerned by precipitates, we're concerned by losses of potency as

that might effect the efficacy of treatment. I don't think we're pushing manufacturers in one direction or another, either toward gylcerinated extracts or towards lyophilized extracts. We have no specific initiative to do that either way.

DR. GRUCHALLA: Two questions. One is where do manufacturers stand as far as glycerinated extracts? We're actually called by our major manufacturer saying that they're going to total glycerinated extracts and I was just curious of that was the same across the board.

And then secondly, you know, one way to get around it when we get the extract glicerinated but then to make your dilutions in something that is non-glycerinated but then you get back to the issue of you're losing, you know, the stability over time. But I wonder how often that is happening in practice, probably more often than not.

DR. SLATER: Well, let me answer the second question before the first question. I don't think anyone is suggesting that when you got to glycerinated extract, you should dilute it up in an aqueous solution and then store it that way but certainly people are diluting glycerinated extracts so that they don't have to give concentrated glycerin

doses. And that's leading to increased volume with injection, increased numbers of injections which is especially for pediatric allergists is a major concern.

Now, in terms of what the manufacturers are doing, I think that probably is motivated by the difficulties posed by the precipitation. I think the manufacturers have recognized when they've looked at their product lines that they have fewer problems with their glycerinated products than with their aqueous products. And the response of some manufacturers but by no means all, has to reduce their exposure by reducing the number of aqueous products.

I don't know, Peter, if you'd like to tell me whether I'm off base on that.

MR. HAUCK: I think you're dead on, Jay. That's a fair comment.

DR. BERGER: I think the issue is that if we make a complex mixture with -- I mean, the issue is that if you want to give as high a dose as possible at maintenance, you wind up giving a high dose of glycerol, if you had a glycerol stock regardless of how you diluted it, either during the raising dose phase or even if you wanted to dilute the maintenance injection.

If you make a multi-antigen mixture, and you're mixing glycerinated with aqueous extract, which lots of us are probably doing, then you're diluting out the glycerin but still having, you know, a lot of antigens. But if more of the aqueous antigens become glycerinated, then we're going to be diluting glycerin with glycerin and it's going to hurt more. You know, it would be -- if you had now a glycerinated extract and a short half-life lyophilized extract, that would be all right because you can make the aqueous solution of the lyophilized extract in your office, keep it for a short time and the final dose of glycerol would not be that high.

But as more products become glycerinated, it's going to be hard for us to have those maintenance mixtures that have a lower concentration or a lower total dose of glycerol at the maintenance dose.

DR. NELSON: Yeah, and I would agree. You know, what's going to happen, it's going to make it much easier for people to administer less than fully effective doses so that in a sense we may be contributing to decreased efficacy of extracts.

DR. BERGER: Right, exactly, because pain rather than immunologic reaction will be the limiting thing on dose.

DR. LEHRER: Any other comments from the committee? Peter.

MR. HAUCK: Jay, you had a slide that said in one series of observations particulates appeared in 95 percent of aqueous extract. Who made that observation?

DR. SLATER: That's actually based on manufacturer's data.

MR. HAUCK: Okay.

DR. LEHRER: Any other comments from the committee members? Now, Bill, with the open public hearing have there been any requests to speak?

DR. FREAS: Again, I have not received any written requests to speak in this open public hearing. Is there anyone in the audience?

(No response)

DR. FREAS: Okay, while we're waiting for a response, let me just remind everybody this will be the last open public hearing of the day as scheduled. There will not be one at 2:00 p.m. Hopefully, we'll all be home by then. There definitely will not be an open public session at that time.

At this time, we're getting ready for lunch. And when we resume after lunch, we will resume in close session, so I will have to ask the cameras to

be disassembled and removed from the room during lunch. I will have to ask that the public not attend the afternoon session. The only people who will be permitted in the room will be those on the committee and those directly involved with the processing of the site visit report.

Any briefcases or personal items left in the room will be placed in the hallway outside of the back door. The Chair has asked that you have an hour for lunch in which case we're going to ask that everybody resume here at 1:00 p.m. for the closed session. So we'll see you after lunch. There is a table reserved downstairs for committee members. If you'd like to sit at a table together, that's fine. It's down in the restaurant right below here. We'll see you at 1:00.

(Whereupon, at 11:50 a.m., a luncheon recess was taken.)

CERTIFICATE

This is to certify that the foregoing transcript

in the matter of: ALLERGENIC PRODUCTS ADVISORY COMMITTEE MEETING

Before: FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION
AND RESEARCH

Date: FRIDAY, MARCH 15, 2002

Place: BETHESDA, MARYLAND

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

Pippa Antonio