extracts, which again were presented at the October meeting, some data generated by both Greer Laboratories and Hollister Stier.

This one is very busy. I don't expect you to get much from the exact values. However, this was a look-see at all the different extracts that were looked at. They looked at the SDS-PAGE and concluded that before and after removal of precipitate, the profiles were comparable.

The resulting phenol content was still within the release limit. pH didn't seem to take any major shifts. PNU -- again, some went up; some went down. Typically, I would say the variability of a NU assay is somewhere in the 15 to 20 percent range. So none of these really feel outside of what you just would see from normal variability.

Another company, and again this was Hollister Stier -- took a look at some vial container products that had precipitated. Again, all negative for the presence of microbial contamination. SDS-PAGE profile did find in two products, a bottle brush and an English Plantain, that there was perhaps a loss of a band up at the 180 kiloDalton range there, and then loss of band definition of 40 kiloDalton.

Also, they reported on a lot of AP Dog

that we were able to quantitate the can F I. With the precipitate two, there were 251 units per mil. After the precipitate was removed by filtration, there were 253.

These are just some examples of the SDS-PAGE profiles that, again, were shown at the October meeting, the p indicating the precipitate was still present, the n meaning it had been removed, no precipitate. Again, removal in this case was done via filtration, sterile filtration for sterilizing membrane.

Since that time, since the October meeting, a little bit more data have been presented or provided by manufacturers. This is an example, a company that looked at the protein content before reprocessing and after. Again, you see some -- a couple go up, a couple go down. This one goes up.

We will be the first to acknowledge the database are quite limited, but I think the point is that overall everything that we are seeing is suggesting there is no major shift in protein, protein profiles or anything as a result of precip.

Some additional data from Greer Laboratories, again looking at some reserve samples, some product lots. In summary, again their conclusion

being that in the overall aggregate, the presence of precipitate doesn't affect the overall characteristics of the extract.

Some additional data since October on comparing PNU, pre-filtration, post-filtration: Again, a few higher, no change, a little lower, a little higher, all again within what I would consider the range of normal variability.

Again just some more examples of different SDS-PAGE profiles on different products, again visually similar. Again, if you look closely, there may be a few bands that tend to lose definition, but I think your eye will tell you that the precipitated and the nonprecipitated look pretty similar.

Just some more examples, some with heavier, more predominant protein bands than others.

Then the last one. There were several agreements that came out of the meeting with CBER personnel in October. One of them was that the manufacturers agreed that extracts with any visible precipitate would not be shipped to the customers.

The second was that the manufacturers agreed to include common verbiage in their product instructions regarding precipitate.

Third, manufacturers and CBER personnel

agreed that attempts to characterize and look at these precipitates would continue and, fourth, to try to standardize the error and accident reporting, which as you heard earlier, is now the biological product deviation report.

So current initiatives by the industry resulting from these agreements that were reached in the October meeting: To inspect the product just prior to shipping to customers, and do not ship the product is precipitate is visible.

The effects of this initiative on both the industry and the patients include: There will be product shortages when the manufacturer must discard the product. They've got their product ready to ship. They collect the vials to fill an order. There's precip in it. The lot will be discarded. That patient will not receive that order.

So these shortages will result in a disruption of product supply, which will ultimately affect the treatment regimes that the patients are undergoing who are receiving immunotherapy with these products.

We all agree, I think, that there will be reduction in product lines as manufacturers will discontinue making these products, the ones that tend

to precipitate almost all the time.

There will be increased cost to the customers to offset the increased losses to the manufacturer, and a move toward the use of glycerinated extracts or more dilute non-glycerinated products.

The agreement to add the verbiage regarding the presence of precipitate: There have been, my understanding is, some discussions between some manufacturers and CBER. One of the proposals is to add wording in the dosage administration section of the instruction, and there is verbiage given in 21 CFR, Section 201.57 regarding the instructions to look at any product for the presence of discoloration or for particulate or precipitate.

This will require submission and approval of each insert used by each manufacturer, although I understand there may be ways to get approval of the wording in one, and then provide annual updates or something. So it may not be every insert needs to be approved, but certainly, the initial one will require preapproval.

Continued evaluation of products with the existing technology, again including protein content, protein profiles, potency assays when it's a

standardized product that precipitates. That may ultimately expand to include immunoblot so that we can actually look at the allogenic proteins that are being affected as opposed to just the total protein profile.

One of the other things we talked about was attempting to work with CBER personnel to expand use to new technologies. This is really in its preliminary discussion stages, hasn't progressed anywhere.

Then the last one, the ultimate goal is to develop alternate manufacturing methods that would prevent the formation of precipitate. I feel this is a very long term project as, number one, we would have to do the extensive studies just to determine what we could do to keep the precipitate from forming.

Then once we were able to do that, there would still be the studies to show the equivalency, that we haven't affected the product in any way. In light of the earlier presentation and the number of patients involved in that, that could get quite expensive.

That's where we're at. Again, like I said at the outset, I apologize for repeating so much of what Jennifer said, but again I think it demonstrates that we are all pretty much working with the same

knowledge base.

So there was a couple of questions. I don't know if they were, in fact, addressed.

DR. SAXON: If I was approaching this scientifically, the first thing I would want to know is how common are precipitates that are visible out of the thousands of lots that are made. I still don't understand. Is this one percent, 50 percent? How big is the issue in that regard? Can you give us any idea?

DR. WILLIAMSON: Yes. We did a survey -- Again, I can speak on behalf of my company. I can't on the total industry, but I don't think we are probably that different.

DR. SAXON: What's the number?

DR. WILLIAMSON: It was about 7.5 percent of the products.

DR. SAXON: So let's say ten percent. Ten percent of extracts have a visible precipitate.

Now the second question to ask: What is the amount of that precipitate? That's easy as pie. If you haven't done it, I'm stunned. You take a little capillary tube, and you spin it, and you measure the amount.

We don't know -- It looks like 80 percent.

I understand what you're saying. It could be one percent. So someone should take the ten percent of lots, get a little capillary tube, just spin them, and you measure the quantity so we know how frequent it is, the quantity it occurs; because this whole thing may be a non-issue.

I mean, the whole thing may be a non-issue. If it turns out that the potency is no different, the quantity turns out to be one percent of material that when you spin it down, or less, and there's no difference, and you could prospectively before you throw this whole thing out -- We don't see short ragweed. We don't have it California. That's why, I guess, I've never seen those.

Yes, we don't have short ragweed in California. No. it's another reason to move there, in spite of the earthquakes.

What you can say is -- So then before you say you can't send this stuff out -- You know, you have now said, basically, this stuff is bad. May well be. But it would be more interesting as a scientist to say, okay, we know this lot has precipitate. We've measured it. It's two percent. We spun it down, and prospectively look what happens to that lot, versus prospectively to its cousin lot.

Ask the manufacturer to do a prospective, active surveillance. You could actually solve the issue. What you're going to do now is say the issue is bad, we must get rid of it. And it's okay, but you're going to add extra expense, and it may be a waste of time. You may be chasing nothing.

So I think getting some data would be better than chasing something that may turn out to be irrelevant.

DR. SLATER: May I comment? I certainly don't think anyone is going to disagree that we need a considerably larger body of data on this question. I'm not really sure that the point was clearly made, and that is that we are actually rather ignorant about the effect that this might have on potency.

The only extracts for which this happens with any frequency at all for which we have any valid potency measure is short ragweed.

DR. SAXON: You mean her data is invalid. She just showed us a bunch of data. I just -- I heard what you said, but you just showed me a whole bunch of other data.

DR. SLATER: Sure. There is a bunch of other data about PNUs per ml. There is data bout pH.

DR. SAXON: It was a huge -- It was 20

percent of the protein was precipitating. It should have been going down.

DR. SLATER: Well, but we know very well that the correlation between PNUs per ml and potency is extremely poor. In fact, you could have a dramatic decrease in the actual allergen content and preserve PNUs per ml.

DR. SAXON: Fine, and you could do that with or without precipitates.

DR. SLATER: That's exactly correct. But for a large portion of our extracts that are precipitating, which is, you know, according to industry data, something on the order of one in ten to one in 20 vials, it is actually quite remarkable -- It's not remarkable. It is a testimony to the importance of standardization to study problems such as these that we are essentially having a problem because only one of the allergens that is standardized -- only one of the allergens that has this problem is standardized for which we have a measure.

Furthermore, Dr. Claman pointed out that, even though as you pool the data you may not have a statistically significant difference, for some extracts it may be more significant than for others.

DR. SAXON: Yes, but again, you didn't do

the controls of all the other lots that may have gone down that weren't precipitated. I mean --

DR. SLATER: I just must differ with you about the concept of not worrying about extracts that have a relatively small precipitate crit. I actually think that I worry a lot less about that slide that Jennifer showed that two-thirds of the bottle was full of precipitate, because -- let's be honest about it -- nobody would inject that into anybody. So that would be one that I'm not worried about patient safety, because I don't think that vial would have ever gotten near a patient.

I am much more concerned about the relatively more subtle precipitates, the kinds that we don't really know what the impact is and that might, in fact, be getting injected.

One of the things that I would really like to ask the Committee to spend at least a few minutes on is I would really like to find out what the sense is of how often you have actually seen this.

I must tell you that, when I first heard about it, having just come from clinical practice a short time before, I had never seen one of these, and I was horrified at the numbers that I was seeing, because it was clear that there were extracts that I

was not aware that these actually had precipitates in them.

So I would really be interested in finding out what the Committee thinks of this.

DR. UMETSU: Actually, we don't use ragweed either, because I'm in California. I'm interested in finding out from -- The question is what percent of the ragweed extracts at Hollister Stier have precipitates?

You gave us seven percent of all extracts, but what about ragweed? What percent of short ragweed has precipitates?

DR. WILLIAMSON: I am trying to think here if I can -- drawing back on what I could say for experience. One of the things with the ragweed is we do have to do stability study on ragweed, and formation of precipitate is one of the parameters that are examined throughout these stability studies.

In reviewing that, I was in some ways surprised to note that at least the products that we have been studying on stability -- and we do one lot a year of glycerinated, one lot of non-glyce -- that again the glycerinated in our stability studies we hadn't see any.

The non-glyce will, but oftentimes -- Now

the non-glyce short ragweed also has a very short shelf life. It only gets 18 months total from the date the antigen E assay is initiated.

So by the time we get the product manufactured, through the process, tested, released by CBER, there is really only several months that we have left to be able to get that product out the door, and then to give the end user at least a year's dating.

Now we have seen in our stability studies occasions where that precipitate was present and showed up right at about that 18 month time point, and then beyond. But I was surprised that in our stability studies we didn't see it that often. However, we are now, again as agreed to in that October meeting, doing the visual inspection of all the extracts prior to shipment, and we are seeing a higher incidence of the products right out of our stock.

I don't know the exact number, but I don't sense that it is much different than the approximate ten percent that we were talking about.

DR. UMETSU: But you mentioned that it's much higher with ragweed versus, say, other types of -- other antigens, or somebody said that.

DR. WILLIAMSON: I think again one of the

questions that was asked was, well, how many do you see. what we looked at was we looked at all the lots that we had in our inventory at the time we did this survey.

We had approximately 1900 lots of product. Now that could have been six lots of short ragweed and ten lots of this and so on. Out of those 1900 lots, that's where we had the 7.5 percent of them showed precipitate, presence of precipitate when we did our survey.

So how many lots of short ragweed out of all the lots that we would make in a given time -- and again, the non-glycerinated is the one that is going to precipitate. Jennifer, I don't know. You picture, I assume, was non-glyce, and really our observations of precip in glycerinated short ragweed is virtually none.

MS. BRIDGEWATER: Right.

DR. SAXON: I want to correct one thing, Jay. I don't care if it's a lot or a little. I'm not worried. What I object to is no data. It's sitting there in the vial. Tell me how much is in there, and then other than spinning it, I bet if you go to a non-visual technique like a big light scatter, you could actually quantitate it.

You could quantitate it in another 20 percent, because there's things you can't see with your eye. So I'm just saying you should get data. Just looking at vials and guessing -- get data on what percent of vials have it by light scatter. I mean, that's where I would start, with data.

I think at the moment it sounds to me like anecdotes and anecdotes.

DR. SOTO-AGUILAR: I would like to ask, are they light sensitive or just temperature sensitive? What makes them precipitate?

DR. WILLIAMSON: That was one of the things I pointed out. That's a question we just don't yet. For the most part, our extracts, once they are packaged -- and we don't package them unless they are precipitate free -- they are put in the boxes. they are put in shipper boxes. So they are protected from light at that time, but then we do see precip down the road.

Temperature: Again, from start to finish there are processing. Our extracts are maintained at one to five except for short durations when they are out actually being filled into final container. So two to five or one to five refrigerated temperature certainly results in the formation of this

precipitate, although some of the studies we have done where we have put product at room temperature as an accelerated condition will precipitate sooner.

So I think there's some temperature dependence, but refrigeration certainly doesn't keep it from forming.

DR. SOTO-AGUILAR: And how about pH? Is there any optimal pH?

DR. WILLIAMSON: Not that I'm aware of that has been developed. That's probably one of the first things that could be looked at, at least in the short term, although I think a couple of manufacturers have done some preliminary studies that haven't suggested that that's the answer.

DR. CLAMAN: One would suspect -- As a non-physical chemist, one would suspect that these are like-like aggregates and homodimers or multimers, and that the presence of the glycerine just decreases the chance for two or more molecules to get together.

Now what about -- Aside from warming them up, which I suspect would do something to decrease the precipitate -- maybe not eliminate it -- what about the use of detergents? What about doing Western blots on precipitates versus soluble material from the same vial, etcetera, etcetera?

You know, like gamma globulin -- Gamma globulin is a sticky molecule. It sticks to itself. Maybe short ragweed is a sticky molecule; it sticks to itself.

DR. WILLIAMSON: And I think those are potential things to look at, but as I had pointed out earlier, one of the biggest difficulties is, even when it looks like you have a lot, by the time you try to get it clean so that you're comfortable you're not getting anything still there from the extract itself, and then try to analyze it, either you've lost it all through the cleaning or it will actually at that concentration redissolve.

DR. CLAMAN: That's good news, too.

CHAIRMAN OWNBY: Well, maybe the idea shouldn't be to clean it, because if this was really an aggregate of some component, you ought to see merit concentration shift, even if you didn't have -- you know, even if there was still some contamination left from the rest of the extract.

I think that we are all pleading with the idea that we need some very basic data. I mean, I think it would be interesting to know just whether this is a time phenomenon, whether now that you are examining all of your lots before you ship them, how

many of them still come back, because I think most of us, the first thing when you saw a vial that was precipitated, you just called up the company and said, hey, you know, I'm sending you this one back because it's got a precipitate.

You know, are you still getting those back that were clear when they shipped, and can you learn anything about the shipping conditions? You know, these all come back for winter shipments or all come back from summer shipments or some of those other basic things. Then just the physicochemical properties of the material that's there.

DR. WILLIAMSON: In answer to your question, he said, well, you still get them back. At Hollister-Stier we implemented our visual check at the time of shipment right at the first of the year, January 2. So we haven't been doing this that long, but that is certainly a parameter we will need to examine and see if there is a correlation, if in fact we do see a reduction in returns now that we are sending them out clear or if the level stays the same, which means they are now precipitating once they leave our hands.

DR. SAXON: The real issue is safety. I mean, Jay is after safety. Right? One way you look

at that is, if it's lost potency, it's not as good anymore. You can answer that pretty straightforward. You should be able to, by looking at --

The other issue which you're going to lose the opportunity to look at is I guess you stop -- you used to send them out when they were -- or has the industry sent them out previously when they had precipitate in them? Okay. Nothing wrong with that, and I'm not horrified. I don't care.

My point is it may be no difference. But when you send them out, you still have an opportunity to look prospectively at what happens. The alert system will never work. No one reports allergy adverse events, because they are part of the natural history of the problem. So we don't report every time a patient gets a swollen arm. Right? But if you took a lot that you knew had precipitate in it or had lots of returns, you should have an active surveillance.

If it's not a problem, then it's not -- That's the only way you're going to get safety data on precipitate versus non-precipitated lots. So you've had lots of it gone out, but you're going to have to actively surveil, not passively surveil.

If it was my experiment, I would do the experiment. I would get a lot that had precipitate or

maybe if you can't do precipitate, you do a light test now, because you know it's got more material that you can't see, but you know it's got more than a cleaner lot. If there's no difference, there's no difference. The data will be the data.

DR. UMETSU: Clearly, there needs to be more data. I would also suggest that perhaps the precipitated lots would be actually more efficacious.

DR. CLAMAN: Absolutely.

DR. UMETSU: So you may actually get a better product when it precipitates.

DR. SLATER: I'm sorry. Are you proposing that as a possibility?

DR. SAXON: Sure.

DR. UMETSU: I think that, if you look at it immunologically, if it's homodimers or homomultimers, those precipitated antigens would be more immunogenic, if that's what you are trying to do. If you're trying to immunize, that's what would happen.

DR. CLAMAN: You don't agree?

DR. SLATER: I am not saying it is. I'm just saying we need more data.

DR. CLAMAN: there's a long history of increased potency of aggregated immunogens versus

soluble immunogens. This may not be what you're after. We're not really sure. But I agree with Dale 100 percent.

DR. SAXON: Before you throw the whole thing out --

DR. CLAMAN: That's right. That's what I'm saying. You need data.

MR. SAUSVILLE: Can I say something here? I'm Bob Sausville with the Office of Compliance at Center for Biologics.

I think our concern would be that a particulate is not -- the precipitate is not a particulate. I mean, can you tell by looking at it that it's not microbial contamination and that it's only something that's some out of solution?

I mean, you've made reference to the fact that it could be microbial contamination or have microbial contamination with it. I mean, I think our concern would be, just because you have this particulate or -- precipitate -- Anyway, what I'm trying to say is you can't be sure that it's only one thing and it's not a combination of things just by looking at it.

DR. WILLIAMSON: And I'll have to acknowledge that's true. Just visually, can a

nonexperienced -- well, even experienced look at it and say, oh, no, that's normal particulate -- precipitate.

In some instances, I would venture to say you probably could, but not in all. However, I will also say that from experience I have had the occasion to see a couple of lots that were contaminated microbially that were perfectly clear.

So, you know, a clinic could have a perfectly clear extract that is microbially contaminated. So whether or not it's fair to say, well, they have been using these extracts for years -- doctors have -- that have this precipitate, and again I am not aware of any instance ever that was reported for a bacterial infection associated with an injection from an allergenic extract and then let alone associated with precip. But that is a point, that visually you wouldn't be able to tell.

MR. SAUSVILLE: Well, I think from a safety standpoint, you know, from my perspective, that's one of the most important. If you can't make that distinction, then you can't just send it out without any concern.

DR. CLAMAN: I have a really dumb question. You have a bottle of extract, short

ragweed. If there were some way to --I guess you could on a column -- remove all the immunoreactive material, all the short ragweed antigens on a column and analyze what was left, what's left? What percentage of what's in the bottle are, in fact, bioreactive ragweed antigens, and what percentage in the bottle are plant proteins that have nothing to do with allergenicity?

I have no idea. I never thought about it before.

DR. SLATER: No, I don't know.

CHAIRMAN OWNBY: Please use the microphone, Dr. Pasteur.

PARTICIPANT: Yes. We actually do have measurements of the protein content versus the potency, and we've seen that for extracts that have the same relative potency, the protein content can vary by over a factor of ten.

So that's not a total answer to your question, but the fact is easily a factor of ten.

As long as I'm standing up, a little earlier you had made the point that, if you gave someone the precipitate, that would be sort of super-potent or, you know, extra good, so to speak.

Well, the problem is, if it's -- it could

also be super-potent, and in that sense it could actually be a very dangerous thing to actually give. So it doesn't necessarily mean that it's sort of good if it's more potent.

DR. SAXON: It's going to be less than ten percent. I mean, at least for things like -- when they looked at Amb a 1 -- Was it Amb a 1? The studies on the graph -- so that's why you get this huge protein change. But if they were aggregated, the allergen were aggregated, it wouldn't be more dangerous. Right, Dale? It would be safer, because it would be aggregated anyway. So it wouldn't make it more dangerous to have aggregated immunogens.

I just think you don't know, and I --

DR. CLAMAN: So what you are saying is it's likely that 90 percent of what's in the bottle is irrelevant to our subspecialty.

DR. SAXON: Yes.

DR. CLAMAN: And therefore, all other things being equal, which they never are, the chances are nine out of ten that the precipitate doesn't have anything to do with its immunogenicity either.

DR. SAXON: Right. And the data will be the data. But, Henry -- I mean, that's why people wanted to then clone antigens, but then it became,

hell, you got to clone ten antigens or 12 and then reconstitute. It ain't worth the trouble. Use the natural stuff. It has a bunch of carrier protein with it.

I just think it's an unknown issue in making any kind of decision. I mean, it looks cleaner. Is it better? Is it worse? I don't know.

CHAIRMAN OWNBY: It just seems like there's so many other components in here that we normally don't think about. We think about the allergens as proteins, but there are a lot of pigments. There are a lot of phenols. There are a lot of other compounds that potentially could be part of this.

I wonder about some of these secondary effects we don't normally think about, like the pH of the glass that this is going into and the surface properties that you get into play. It seems to me that this would drive a physical chemist wild for a while to try to figure out where these are coming from.

DR. SAXON: Wouldn't you be more interested to know if they were even worth worrying about? See, that's my concern, because if they are not worth worrying about, I wouldn't waste my physical

chemist's time and money worrying about them. If they are a problem, then they shouldn't be used.

CHAIRMAN OWNBY: Well, if you are throwing away whole batches of extract, it becomes a pricy problem. It needs a solution.

The one thing we haven't touched on is what do physicians do in practice when they get these? I mean, if they see it initially, I think most people send it back. The question is what happens after it's in a treatment set and you see precipitates, what do physicians do?

MS. BRIDGEWATER: Shirley, I'm wondering if you could comment on that a little, about percentage of returns you get versus how much product you send out.

DR. WILLIAMSON: Again, we track our returns. Anytime we get a return for a precipitate, we have a procedure that we follow. One of them is looking at how many other vials from that lot were manufactured and have been shipped, and especially now with the biological product deviation report that's a part of that report.

To be honest, what I've observed in evaluating these reports is we may have had a lot of 50 vials from a given extract and gotten two of them

back for precip, and never heard on the other 48. Yet in my experience, again I have seen that it's very unlikely that out of a lot of 50 you would only have two precipitate. If two precipitate, they have all gone.

So to be honest, I think in the majority of the cases -- and I think it's a matter of -- they are used to it. It's a problem, as I said, we as an industry -- and not just us but the medical community also that uses these products -- have seen and recognized.

It used to be that, you know, people comment -- or the gal that handled the technical service reports would say, oh, must have a new nurse in Dr. So and So's office, because I'm getting complaints on precip. And it would be -- yes, it would be cyclic. But you kind of, oh, they're not used to seeing this, and so they are returning it. Once they get used to it, we won't hear from them.

DR. SLATER: So, Shirley, would you conclude form this that the physicians even know?

DR. SAXON: Why don't you ask at the AAII meeting? The FDA can get in touch with people that order them, and find out.

See, the other thing that concerns me,

Jay, about this is that the concept at the human eye level of precip means something. I tell you, if you use optical techniques, you'll find 30 or 40 percent. Then what are you to say? Well, we've regulated at the level of the human eye?

You know, maybe you should regulate at a much more objective level, but you can set it by flocculation. So before you get into that whole mess, I think you ought to figure out what's really going on.

DR. CLAMAN: See, you missed the point, Andy.

DR. SAXON: Yes, I always do.

DR. CLAMAN: Our Chairman said it and didn't realize that he said it. He said this is something that needs a solution.

DR. SAXON: Right.

DR. SLATER: If I could just come back to a point that was made a few minutes ago about the aggregates perhaps eliciting better immune responses, just recall that unless the aggregate happens to be made of the target allergen you're interested in, you may now be generating a good antigen for an immune response that is undesirable or perhaps competitive.

DR. CLAMAN: I said it mostly to be

provocative. I think we ought to find out what these precipitates are made of.

DR. SLATER: but I think most critically is that the appearance of the precipitates is an uncontrolled phenomenon. It's a phenomenon on which, even within a given product line at a given manufacturer, may be relatively inconstant in terms of its degree and in terms of its composition.

I mean, I think it should be stated explicitly that the precipitate in product A is almost certainly a different molecular entity than the precipitate in product B and, for all we know, precipitates within product A may be variable in terms of their precise composition.

So I think it has to get into the record that we can't sort of accept this degree of uncertainty as a neutral event without knowing more about it.

DR. CLAMAN; I agree. You could be on very weak ground if you ignored it.

DR. UMETSU: Yes, I would agree. When I mentioned that it might be more immunogenic, I'm just saying that we need more data. We need a lot more data. We need to find out what is in the precipitates and what causes them to precipitate in some lots, some

vials, and not others.

DR. SAXON: I am uncomfortable. I agree, but it's been five months, October, November, December, January, February, March. This is six months, and this is what we know. It's nothing.

I mean, again, you could go and start measuring the amounts of this in ways and have data within a month. It seems like this has been going on for six months. I'll be gone and this will be going on in four years, and you still won't know anything. There's no plan.

CHAIRMAN OWNBY: Are you going to propose a plan for us, Andy?

DR. SAXON: No. I think Jay raised this thing. They ought to have -- He should come back next time with a plan and some data. I'd tell the manufacturers, spin it down, give me numbers, get some data together that they think is believable, and see if it is an issue or not an issue before they start making decisions based on anecdotes -- anyone makes decisions. It's definitely of concern to all of us.

CHAIRMAN OWNBY: Jay, it would also seem not that oppressive to ask the manufacturers at one of the professional meetings to ask physicians and nurses who handle these what they do with them. How many of

them look at their extracts. If they see something, what do make a decision?

I think we've heard suggestions that, oh, well, once they are used to it, they just go ahead and use the stuff, even though they see it's a precipitate, because they don't consider it a problem, and others that may well be discarding all of this or sending it back to the manufacturer in some variable level.

DR. SAXON: Now you've got the manufacturers throwing it out. Right? So maybe they should send it to you instead of throwing it out, and you can measure the precipitate amounts. I mean, that would be the very first thing to do.

DR. CLAMAN: I think this is appropriate both for the Practice Standards Committee or, as far as the Academy goes, for the State and Regional Societies. They love this kind of thing, and it's very practical, and they could come up with some information probably pretty fast.

DR. UMETSU: One could also do some mouse studies to compare the precipitate version versus the unprecipitated version to get an idea of immunogenicity.

DR. SOTO-AGUILAR: I have just one

question. You said that the precipitate might look large, but when you measure it, the volume is negligible or is very small.

Is that because the cloudiness is occurring at the glass side, in contact with the glass? So it makes it look larger, but in fact the volume is not that large.

DR. WILLIAMSON: I think it may be related to several things. Number one, as you're looking through a volume, even though it looks like there's a lot there, it may be that there's some distortion through the class, but also especially the flocculent ones are the ones that are the most surprising.

You look at them and you think, oh, my goodness, there's a whole bunch of stuff in there. We're going to get, you know, layer when we centrifuge this down. But once you get it compacted down, the liquid is removed from it, it just isn't that much there. And whether it's illusion or just the fact that when it becomes diffuse, scattered throughout the solution, it appears to be more there than there actually is.

Just one question, if I may. The suggestion was put forth for the industry to poll physicians such as at the Academy meeting. I don't

think the industry would have any objection. We could certainly set up something like that. But I guess my mind goes to the next step. What would you do with that information? How would that impact where we're at right now and how we would assess potential impact or what do we do with these products in the future?

DR. SAXON: I don't think just polling them like in March is going to help, because it's tremendously biased. I think better is you've stopped sending precipitate out -- precipitated visually in January? I don't know what the -- But if that's happened, then you -- what you want to do is prospectively.

You've got to have a good study, not anecdote. You've got to prospectively tell your customers to look for it over the year prospectively and see what you're getting, because otherwise it's what do I remember. But if you're going to actually set it up to prospectively look at it, say we will be sending vials; please notify us if you see this.

You don't have to say send it back, because some of them -- you know, you'll find out what their custom is. I mean, tell us what you do with it. Then you'll find out who keeps it and who doesn't. But it needs to be done prospectively. Just sort of

a questionnaire is anecdote.

MS. LIBERA: Do I understand that there's no -- you haven't made any correlation between adverse effects on patients?

DR. SLATER: No.

DR. SAXON: They don't get enough reports on that to make that meaningful, I understand. Right? People get swollen arms all the time. So who would know.

MS. LIBERA: Maybe that's why immunotherapy takes so long.

DR. SOTO-AGUILAR: Another possibility: If you use a vial that's been used, is open already, has been interfered at times with needles, could air, entry of air into the vial confer some chemical property that changes into a physical property with flocculation or precipitation?

DR. WILLIAMSON: Again, that's always a possibility. That may have some impact on the rate or what exactly forms. However, we see it in vials that we have filled that have been sealed, that have never been entered. In fact, when it's still at our facility, that's the form that's it's been in when we see it, and we'll discard the product at that time.

So I don't -- The mere introduction of air

or the mere reduction of volume within the vial is not the sole cause. As I said earlier, again in the years that I've been involved with this industry and one of my first projects when I started with this company was to look at precip, we have a product that's unique to Hollister-Stier, which is AP Dog.

I think the studies on the Can f 1 content and a number of other things have certainly demonstrated it is the most potent, but it is very prone to precipitation.

The only study I think I ever found out was that the only way I ever stopped precip from happening was to make an extract just to study the precip. It wouldn't precip. But the characterizations, the differences that you see are so varied.

That's why I guess -- and I'll carry a bias with me from the years of experience that I've had, but I truly believe that there's a multitude of factors that are involved of which we haven't identified probably a single one, other than -- I believe concentration is certainly an impact, and in some instances it may be a function of just the solubility. You've literally reached a saturation point, but I don't believe that's the case with all of

them.

So it is really a difficult problem to wrestle with, to try to solve it, when you -- at least I don't believe there is a single causative factor.

CHAIRMAN OWNBY: When you say concentration, also whether or not it's in glycerine.

DR. WILLIAMSON: Right.

CHAIRMAN OWNBY: If it's in glycerine, it's much less likely to do it.

DR. WILLIAMSON: Correct. Although there are glycerinated extracts that we will see precip in.

CHAIRMAN OWNBY: Okay. We also have a period here for public comment on this issue, and I was wondering if there is anyone else who wanted to make a comment concerning this. No one else wants to speak up on precipitates?

Okay, any other questions or comments from members of the Committee?

DR. SLATER: If I can just summarize this discussion.

DR. SLATER: We've been waiting for this, Jay.

DR. SLATER: No, I just want to make sure that I'm getting all the messages loud and clear.

It seemed to me that there was some

consensus that we need more data. Am I correct with that? And among the data that we are lacking are data on the prevalence of the problem, data on the sort of quantitative severity of the problem on an extract to extract basis, perhaps by somehow quantifying the amount of precipitate either by simple centrifugation or perhaps by other light scattering techniques.

There is some sense that we could benefit from some animal immunogenicity data comparing extracts that are precipitated and non-precipitated. I think I heard that there was some need for better physicochemical characterization of the precipitates themselves.

Then in terms of further data, there was some interest in obtaining at least prospectively some idea of how often physicians encounter this and what they do with it when they do encounter it.

DR. SAXON: After January, just because they sort of changed after January, and you might get a confused picture. Right?

DR. SLATER: Is there any other message about studies, because I think one of things we were looking for were kinds of studies and the kind of information that we would need.

DR. UMETSU: There might be some

usefulness for safety data that correlates with the precipitate or absence of precipitate in terms of reactions. But how I see the problem is how you're going to get that. But at least that would help. That kind of data would help.

DR. SAXON: I have a suggestion of how you could get that. One of the other things you skipped was your work on the potency. So the manufacturers are going to pull lots with precipitate now. Right? So what you've got now, what do you do with them? Throw them out? Send them to Jay. No, no, I'm just kidding.

What I meant is the concept is you have very limited data that you were saying about potency changes. I mean, if it doesn't change the potency and doesn't change the safety, then it's not a very great concern. If it does either of those others, it's of great concern. Right?

So you have the opportunity to look -- continue your data on precipitates. Don't you think that should be done? You didn't have that on your list is why I mentioned that, Jay.

DR. SLATER: It's on my list right now.

DR. SAXON: Okay. The other is, if you are going to send it out to docs and say, okay, we are

sending people out -- or materials -- and did you see a precipitate. Then if you didn't return it, you can then also then go back and look at prospectively the reaction rate in those people versus the people where they, you know, didn't get -- who got another lot that didn't have precipitate or didn't see precipitate.

I mean, it's not a simple study, by any means, and it's going to take effort and ascertainment and someone to follow up. It's not a passive system, but that's the only way I could think of.

The other way was to send out lots with precipitate and lots without precipitate, which you stopped doing now, and then prospectively just canvas all the doctors and find out, and you'll know which ones got precipitate and not. But you stopped it.

CHAIRMAN OWNBY: Shirley, is it my understanding that when you -- Normally, you manufacture lots that are fairly large, several hundred vials at a time. Is that correct?

DR. WILLIAMSON: It depends on the manufacturer. In our case, we tend to -- after the product has been sterile filtered -- hold it in what we call a stock concentrate form, which are in larger containers, and then dispense into vials.

CHAIRMAN OWNBY: Your stock containers are

what, 500 ml or several liters? I mean, what kind of volume are you talking about?

DR. WILLIAMSON: They are either 150 or 500 ml bottles that hold the stock concentrate, and our lots size for our final container product will range from 18 to several hundred.

CHAIRMAN OWNBY: Okay. And you are saying that usually, if one of those bottles develops a precipitate, all of them will develop a precipitate?

DR. WILLIAMSON: Yes.

CHAIRMAN OWNBY: So this seems to be a manufacturing lot phenomenon rather than after the extraction, the filling or handling after that point?

DR. WILLIAMSON: That's correct.

CHAIRMAN OWNBY: Okay. And the one thing you've never been able to figure out is what's different between one lot to the next that allows this lot to precipitate and the previous lot didn't?

DR. WILLIAMSON: That's correct.

CHAIRMAN OWNBY: And most of the time, at least with large things like grasses or rag where you handle a large volume, you're -- probably blending isn't the right term, but you're using multiple lots of mixed pollen so that you try to maintain some stability of your initial material that you then use

for extraction. Is that correct?

DR. WILLIAMSON: Okay.

CHAIRMAN OWNBY: Well, I mean, you don't use just ragweed from one field one year to produce a lot of extract. Usually, you have multiple years together. You don't?

DR. WILLIAMS: No. Again, generally, we'll hold to the first in, first out. So we will be using up our inventory based on the oldest material first, and collection sizes for pollens can be fairly extensive, and we may get 10,000 grams from a given collection lot. That in itself will make several lots.

Then what happens is we get to the point where we have some left over, and it's not enough to make a full size lot. Then we will go to the next oldest lot, combine those to make the extract. But it actually is probably more common to see only one or two raw material sources in a given extract lot than it is to see multiples.

DR. SAXON: I have a suggestion for the manufacturers. It will be interesting to take your material and just do an optical density on them, a light scatter. You may be able to predict, you know, before they precipitate. You may have data in there

when it comes out, you can say this one's got an optical density of this, it looks clear. And you say, hey, this lot is going to precipitate.

Then you will at least follow that. So if I was in the business, I would do an optical density as soon as they got off that lot. You may then actually have -- you don't know what's in there yet, but you at least have a predictive test, and it's almost free to run light source through something and measure the light scatter.

CHAIRMAN OWNBY: Except you have to document it, keep track of it.

DR. SAXON: Just don't tell the FDA.

DR. WILLIAMSON: I didn't listen to that.

CHAIRMAN OWNBY: Okay. Are there any other more comments? Any other items of business or for discussion today? Jay, did you have anything else you wanted some non-advice on?

DR. SLATER: No, I think I've gotten very good advice and lots of it.

CHAIRMAN OWNBY: Okay, then I believe we are adjourned.

DR. FREAS: I would just like to thank the Committee members again for coming today and, Dr. Ownby, for your brilliant leadership.

We're going to miss our three departing members, and we'll see you at our next meeting. Thank you.

(Whereupon, the foregoing matter went off the record at 3:13 p.m.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Meeting of the Allergenic Products Advisory Committee

Before: DHHS/PHS/FDA/CBER

Date: March 5, 2001

Place: Bethesda, MD

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