slides. If the Panel would like to take the time to review much more of that histology data, we can certainly take ten or fifteen minutes out and work through some of that data and be happy to work through that production. So if that's a request that you or the other panel members have, we would be happy to go through that.

What we see on histology as you describe is immediately upon injection a macrophage infiltration that predominantly is there to break down the gel. We find a macrophage driven degradation of the gel, the deposition of new collagen formation over time as the gel breaks down and I showed you only a single time point but we can look at serial time points for multiple species if you wish to do so. But that macrophage infiltration is present. It does subside over time. It is related to the mechanism we believe predominantly of breaking down the carboxymethylcellulose in our gel carrier and the deposition of new collagen formation occurs through that process around the particles and then obviously settles down over a matter of months.

So again, Dr. Li, if you would like to go through some of that information, we would be happy to do so.

Per your prior questions, you had asked the question regarding calcium composition and also the question regarding complaint rates and I wanted to get back to you with information on both of those. The calcium composition, the exact method of synthesis of our materials we do consider to be proprietary. I can tell you that the ratio of calcium to phosphate is 1.67 which is my understanding from my manufacturing colleagues consistent with standard calcium hydroxylapatite materials. But as to how it's manufactured, if you would like to go through further information on that, we would be happy to work through the FDA to determine a mechanism to get you that information in much more detail in a private setting because we consider that to be proprietary information as to how we manufacture our product that would be competitively sensitive.

Your second question regarding lip nodules and other nodules and the complaint rates, I

believe the complaint rates for both materials or for both nodule reports categories were approximately 0.03 percent which is a very low complaint rate associated with the shipped units on a worldwide basis. The material is being used for a variety of applications.

One of the challenges in interpreting that data is that the category of other nodules is a catchall category that is not distinguishable as to whether those are lip nodules or in other sites or in what tissue type because complaints may come to us from any number of sources. We could receive a complaint via an email on our website. We could receive a complaint via a phone call from an individual who may or may not be knowledgeable of the exact events that occurred in the patient and so we are limited in how much detail we capture and any time a reference is made to a nodule if it's not specifically described where it is it would go in the Other Nodules category, but in fact, many of those may be lip nodules. It might in fact be specifically related to that application, but they weren't

described specifically with the location identified and therefore would not go into the Lip category. So it's just very difficult to determine what the specific sites of those other nodules would be because of the limitations of any complaint handling process that were limited by the data that we get.

MEMBER LI: Can you tell me if you yourself make the hydroxylapatite or do you purchase it from somebody else?

DR. BASTA: That I also would consider to be confidential information.

MEMBER LI: Okay.

DR. BASTA: Just again, I would be pleased to work through that with you in a closed setting where we discuss the source of the material/

MEMBER LI: I understand.

DR. BASTA: And discuss all of that information, but it is competitively sensitive information.

MEMBER LI: I understand.

CHAIRMAN LoCICERO: Thank you. Dr. Leitch.

MEMBER LEITCH: Well, many of my questions have been addressed as well, but I still want to get back a little bit to the feel of the material on palpation. It seems like at least the photos we have to look at there's not visible nodularity. But I guess the issues I would have, in the long-term we heard from Dr. Carruthers that the one year injections there was a stiffness to the tissues at that point and then Dr. Silvers does have 18-month followup. So if you did an 18 month injection, is there sort of the progressive? If you've done three or four injections, do you get a progressive sense of thickening of the tissue to the feel, the palpation?

DR. SILVERS: I can actually answer that outside the study because I had utilized the product off-label in the past. So I have injected a couple of patients and a couple years later have come back to have more injection done and the ease of injection was not a problem. So fortunately I had had the experience utilizing the material before.

The feel of the material at 18 months,

again the face also feels soft and natural. We have not done 18 month injections. So we have not - we don't have that experience at a year out to see how the material feels, but I do have that experience personally in my practice and I've not found difficulty in resistance.

MEMBER LEITCH: In the extension of the study, would you be or maybe in light of this discussion it seems like perhaps in your evaluation would you try to do something that would kind of address this question because I think people are having the concerns that it's not being addressed in a way that we can evaluate, say, what's the texture of the tissue and the ease of injection with subsequent injections. And obviously some of it may be it may exist that there's more thickening, but if the patients are perfectly happy with it based on the appearance then that's something you accept, a tradeoff that might be acceptable. But it's not really addressed very well in the information we have to look at.

DR. SILVERS: Right. But, as we do

inject more and more and as there is more volume there, there can be a little bit of resistance with injection and we have both found that. It's not difficult to inject. It's still easy to inject but not as easy as it was on the initial office visit.

As time passes and as years pass, it's really as if nothing was there because the material does completely disappear. So it does address the scar question, is there scar tissue there. I have found at least in my practice that after a certain period of time, and I can't quantify that, that it's as if nothing was done. So most of the material seems to be gone and there is no scar tissue that remains behind.

And I think one of the advantages of extending the study as long as we're going to to 36 months is to help us determine what is the face going to feel like, what is the material, you know, injecting material going to feel like after that amount of time, and it will give us those answers in followup.

MEMBER LEITCH: And so, and this may be

also with Dr. Carruthers, when you do these secondary injections more like at the twelve month time period, I guess I would say or maybe even six months, does the material dissipate as well in the tissues or does it bunch up because you are having more difficult infiltrating and more scar tissue?

DR. SILVERS: In my hands, it dissipates fine and what we need to do is we'll inject where the material is needed and that's the most important thing. We're not just expecting to inject it in one site and have it spread all over cheeks. In this case, we have material that remains. The patient's face is much improved and we have a couple of areas where the material has resorbed a little bit and those are the particular sites that we're going to want to go ahead and inject.

So we don't find ourselves injecting such large volumes. There are smaller volumes of material injected and those volumes that are injected are easy to inject in those smaller areas.

MEMBER LEITCH: Okay. Then I have some questions. I think they're probably Dr. Liebeskind

about the radiology issues and I guess I just want to be sure I understand about the timing of the CT films. It looks like at twelve months you have some films when the patient comes in to be seen for their twelve month visit and then a post twelve month injection. Is it the person is injected at twelve months and then you have another film after that?

DR. LIEBESKIND: This study was designed approximately a year after Dr. Carruthers's parallel Canadian study had been implemented. So we have the benefit of patients who were more than twelve months post their therapy. So as Dr. Carruthers demonstrated on the time line, our twelve month, our long-term initial CT scan is greater than twelve months, actually between about twelve and fifteen months period post first injection. Those patients then came back to Dr. Carruthers and he could probably better give you the distribution of exact patient times and their scans were coordinated within a week of their visit to him to his clinic.

MEMBER LEITCH: And so there are no films from let's say the very first injection given to the

patient, an immediate post injection film. Correct?

DR. LIEBESKIND: No, we do in fact. Actually I can show you that time line slide again. I think that will help to clear this up. There were two cohorts of lipoatrophy patients that we looked at. The so-called long-term group is a group that we started to evaluate with CT and x-ray more than twelve months after their initial therapies and that was at the Agency's request. We had this cohort that was in Canada that had been treated for a year.

At the same time, we took patients who were being treated for lipoatrophy. We called this in our presentation the short-term group, but in fact what we did is we had CT and x-ray prior to their injection and then less than one month following.

MEMBER LEITCH: And they would have only had one injection.

DR. LIEBESKIND: Right.

MEMBER LEITCH: These short-term people.

DR. LIEBESKIND: Correct.

MEMBER LEWIS: Okay. So getting at that then, it seemed at looking through the films there

were some where the material was rather bunched.

DR. LIEBESKIND: Right.

MEMBER LEITCH: And then there are pictures where it's in streaks.

DR. LIEBESKIND: Correct.

MEMBER LEITCH: And so my question was if you had a patient who had injection number one and it was bunched and then you had a film six months later, would it be more in a streak as opposed to bunched up?

DR. LIEBESKIND: Dr. Carruthers may be able to answer this a little bit better because his presentation was designed to correlate both the clinician's perspective as well as the radiographic evaluations since it is his patient group that we looked at. But my impression of the study from what I've seen of the images and from what I've heard from Dr. Carruthers is that he massages his patients and so that may also affect not just how he injects the material but also how it gets distributed.

MEMBER LEITCH: Yes. Because one of the questions of this migration issue is whether you have

the bunched up thing and then if you get the streaks if you're actually having a migration and that's how you're getting this streaking up here (Indicating) is related to the beginnings of migration. Now ultimately, migration if your marker is so small it's undetectable, I mean obviously on these CTs you're not getting star burst effect from the amount of calcium.

DR. LIEBESKIND: Right.

MEMBER LEITCH: So it's -- I mean the more it migrates and thins out the less able you would be to see it on imaging.

DR. LIEBESKIND: Perhaps but let me go back to a couple of these examples just so that we can see this. This is, for instance, a lipoatrophy patient twelve months following and there is some material that is present. Let's say this is where we're slicing through the mandible back here and the masseter, this is a bone window, so you're not seeing the muscles as well but just at the margin of the masseter, more than twelve months after the initial injection and this is a huge volume for our study.

In fact, this is the patient who received 34 milliliters. So this is a massive amount compared to many of these patients and as you see in the followup, this is following the touch-up that Dr. Carruthers did after the twelve month study, after the injection following that visit, and you can see that the material really is where he placed it in the short-term. It's not particularly behind.

The clumped versus streaked, I'll show you a couple, just if you don't mind me going back to a couple of the examples that I showed earlier. I didn't find radiographically a distinction in that. I mean I think that there's a difference of appearance. This is a long-term patient. I'm sorry. The patient we were just looking at was a long-term group patient and you see that twelve months later and then following the touch-up is the sort of clumped appearance.

This is a long-term patient and you can see somewhat of a faint streaky appearance where the material is, but also a faint streaky appearance in this patient when Dr. Carruthers did his followup.

So in part it may be the aesthetic look he's going for in the patient either a combination of massage or injection. He would probably be better suited to answer that question.

But even some of these short-term patients have a variety of appearances. This is a short-term patients. So this is before injection, following injection and as you can see it depends on where it's injected. This is actually relative to some of the examples I've shown you fairly posterior accumulation of material - so, and fairly sheet-like as opposed to clumped. And to look at another short-term example, this is a very clumped appearance, even less than one month following injection.

So as a radiologist, I wasn't able to discern a pattern looking at these images as far as migration. My impression was that there was likely some correlation with the intended cosmetic effect and some correlation with either the manipulation, the massage, or the method of injection and I think Dr. Carruthers can probably help you a little with that.

MEMBER LEITCH: Okay.

DR. CARRUTHERS: I agree with Dr. Liebeskind. I think that you are seeing differences in injection patent related to the clinical appearance of the individual. People will often focus on the cheek posterior to the nasolabial fold as being the area where we see the most dramatic lipoatrophy. But in fact, of course, as you're well aware these individuals have loss of fat over much of their face, so that in a study such as this where we're attempting to improve the entire cheek area, then it is very common to go out towards the zygoma and the area below the zygoma because they get parotid hypertrophy and so you're often trying to soften the parotid hypertrophy. So you'll put relatively small amounts around the zygoma and anterior to the parotid, whereas the big chunks are going into the micro-atrophy area and I think that that correlates reasonably well although we've not done a subject by subject correlation of the severity, etc., with the radiological evaluation because the radiological evaluation really was to

answer different questions and it has raised some interesting other questions for us.

MEMBER LEITCH: And I'm not sure who should answer this, but I think we've heard from the presenters several times a mentioning of off-label use and it seems that you recognize that the nodule formation is an issue in some of the off-label use. What are your plans for addressing that?

DR. BASTA: Your question raises a very delicate balance that every company in this industry has to strike in this process. We clearly are aware that physicians are using Radiesse currently for a variety of applications beyond those that are currently approved. They are also using Radiesse for a variety of applications that are beyond the two that are before the Panel today and so there have been reports of use obviously on lip augmentation, in a variety of facial structures, in other body parts beyond facial applications.

One of the things that we attempt to strike balance in as a company is to be careful to comply with FDA regulations and not cross the bounds

in terms of product promotion but in response to inquiries from physicians be able to provide sufficient information that physicians are informed about peer-reviewed literature, appropriate medical practice that their colleagues have developed and the delicate balances that we want to act in the interest of patient safety and provide information such as the fact that Radiesse can be lumpier in lip augmentation than other dermal fillers and so one should be careful about use in that area and certainly this may not be the appropriate product in its current form for lip augmentation.

We need to appropriately inform physicians so that they know of those risks but do so in a manner that doesn't cross the line to initiate conversations about applications that are off-label. We attempt to work through that balance primarily by distributing literature from other physicians, peer-reviewed literature, in response to questions from physicians. We find that that's per the Supreme Court decisions. That appears to be a safe ground in being able to respond to the questions to address

that issue, so that that would be a mechanism for being able to address the issue to inform physicians of the fact that lumpiness could occur there while being careful to not promote in that indication and it's just a delicate balance that everyone in our industry has to strike.

MEMBER LEITCH: Would you say it's contraindicated in the circumstance of doing lip augmentation?

DR. BASTA: I would indicate that we haven't done sufficient clinical work to know best practices or procedures that would be optimal for lip augmentation. I do know physicians who have used the product satisfactorily and have been delighted with it. I also know that there is a higher rate of reported nodules in the lips, to use that term, with Radiesse or at least a longer lasting rate of nodule formation potentially in lips than seems to appear in the peer-reviewed literature regarding other fillers.

But I don't know that it's contraindicated. I don't know that scientifically it is in fact a higher rate or if it's simply reported

more frequently because they tend to last longer because the material lasts longer. We haven't done any good science. We've not done any clinical studies in lip augmentation with this material. We don't have the scientific basis for specifically answering that question. So I believe that our responsible approach as a manufacturer is that if a physician indicates that they have an interest in doing a procedure for which there isn't adequate clinical data from IDE, FDA-regulated clinical studies, then we can at least direct them to peer-reviewed literature where they can learn what their colleagues have done so that they are appropriately informed about making their medical judgments.

MEMBER LEITCH: Okay. Thank you.

CHAIRMAN LoCICERO: We recognize that so far this morning the interrogation has been intense and it continues. So we're going to take our break now and come back at 10:45 p.m. Off the record.

(Whereupon, the foregoing matter went off the record at 10:35 a.m. and went back on the record at 10:54 a.m.)

CHAIRMAN LoCICERO: On the record. Okay. We're going to get started again. We have a few Panel members to ask their questions before we have the FDA presentation. Okay. The next one is Dr. Newburger.

MEMBER NEWBURGER: I would like to address the off-label promotion of this at another time in the interest of expediency, but I'm aware that it has been promoted aggressively since 2003 and I've brought some of these materials with me today.

My first question is for Dr. Liebeskind. Perhaps you could help me interpret Table 47. I know that your conclusions were that there was going to be no confounding of this material for malignancy or a benign tumor nor that it would mask any results and yet when I'm looking at Table 47 for Evaluator 1 it says "Likelihood material falsely interpreted as malignant tumor" and in Group 2 it's 37 percent, Group 4, it's 33 percent. "Likelihood material masks malignant tumor," Group 2, it's 41 percent. I don't understand how you got the conclusions from this particular evaluator who has a high heightened

awareness.

DR. LIEBESKIND: Yes. I think if you look at the datasets that one thing that is quite clear is that the two evaluators have very different individual interpretations and I think that's very useful to us because it does a couple of things. I think it reflects what's likely to happen in the real world in the radiology community when patients come in for imaging and don't have a disclosure, for instance, that prior, we always ask patients have you had a prior medical procedure or prior surgery. Cosmetic procedures like this are the ones that they're most likely to under report.

I think the important thing to keep in mind is what usually would happen in the event that a radiologist was hyper-aware and was, for instance, raising a question like this. What happens in clinical practice as opposed to when a radiologist like this person is blinded as to the underlying conditions, the study, etc. of the patient. In other words, there is the opportunity in clinical practice to ask patient about underlying medical conditions,

calcium metabolism, things like that, what prior procedures they've had to also then especially because as radiologists we are duty bound to communicate an unexpected, significant, positive clinical finding with the referring physician, that the first thing that happens if the radiologist still thinks there's something there, if they have the opportunity to consult with the patient or don't, they then would in the clinical pathway, they would next call the referring clinician and say "Hey, on your patient in this area, I'm concerned. There's something abnormal. I don't know what it is. Perhaps could there be a tumor? Could there be a foreign body? Could there be" --

And at that point somewhere down the line, the fact that this patient has been at least once and possibly serially injected for a cosmetic purpose should arise, even if that doesn't stop any further work-up and with most reasonable mentally aware patients it really should stop any further evaluation, probably the most downstream, likely potential complication for that patient would be a

fine needle aspiration, in other words, probably the sonographically guided, possibly clinically, but at that point the pathologist would be able to see the size of the material that is being described. In other words, there would be no evidence for a tumor under the histology. And utilizing a 27 gauge needle, ultrasound guided light blade, that's probably the worse case scenario even in the event that those questions are answered that way. And taking that in light of the other evaluators' responses, that's one of the reasons that we did not emphasize that evaluator's responses.

MEMBER NEWBURGER: So why is there the statement, the conclusions, drawn from the study where and then the third bullet "there's virtually no risk that the presence of Radiesse will mask underlying structures or abnormal growths in the area in which it is injected"?

DR. LIEBESKIND: I'm sorry if I don't -- Would you mind repeating that?

MEMBER NEWBURGER: The executive summary page, it says "there is virtually no risk that the

presence of Radiesse will mask underlying structures or abnormal growths in the area in which is is injected."

DR. LIEBESKIND: Right, and I think one of the other things that I neglected to mention in my response just now is that many of those questions that were answered positively by that individual were in response to the question on x-ray, not necessarily the question on CT scan.

So I think that going back to the clinical work-up that would likely happen even if you had a hyper-aware radiologist who became concerned about the presence of this material is the next step would be likely a CT scan first.

MEMBER NEWBURGER: So if you have a patient who can give a history, then there's virtually no likelihood that it will be misinterpreted.

DR. LIEBESKIND: That's my feeling clinically. As a radiologist, we routinely see people with all sorts of foreign bodies, devices, as you can see the dental hardware, all sort of other

things. So the one point is to correlate with the patient if the patient can give a good history. And the second things is that as something like this gets out into the community and radiologists become more comfortable with seeing this appearance, the potential continues to go down that this could be confused with anything.

MEMBER NEWBURGER: And CT scans are done on patients who have very severe medical issues and that is not most patients with HIV lipoatrophy. But everyone gets dental x-rays and apical wing x-rays and what will this do? Will it conceal the possibility of a periapical absess or some other sign of dental infection? It seems to me that that is a much more likely and mundane, but significant possibility.

DR. LIEBESKIND: As a practical matter, we're seeing the use of CT scan much more, for instance, than x-ray. The x-ray concern exactly as you say was prompted because of things like dental x-rays, things where they may be a density at the margin of a film and we don't, from the x-ray images

that we have, as you can see it doesn't appear that Radiesse compares as far as density to enamel which is clearly far, far more dense, has very great visibility.

Many of the images that were evaluated, the evaluators frankly either didn't see the Radiesse and in fact, we actually had situations where the evaluators thought they saw something, a foreign body, before it was even injected. So the x-rays were entirely vague when they were interpreted in a blinded fashion and I think that the fact that they were seen, that the Radiesse was seen, so rarely and so inconsistently significantly reduces the likelihood that they would be confusing on a dental x-ray.

MEMBER NEWBURGER: But you didn't look at dental x-rays which are very specific?

DR. LIEBESKIND: Correct. We did not look at dental x-rays.

MEMBER NEWBURGER: Okay. I have another question which again relates to the histology that my colleagues on the Panel have brought up. What human

histology do you have? I'm aware that you have a lot of pre-clinical studies. The reason that I ask is I'm really unclear still as to the mechanism of action of this filler. I don't know whether it is taking up space and certainly there is persistence of the material for some patients even out at a year or if it is fibroplasia.

I don't have a sense of how this is interacting in humans. The only thing I could find in our packet here was the biopsies of the three retroaricular aliquots of the material that were placed by a physician and then biopsied six months later. There's certainly a different interspecies. There is certainly a different in terms of the position placement of a product.

I think that we've all seen with PTFE, with soft form, with Gore-Tex. If you have this product in an internal position, it's going to behave very differently than if it's in the skin. We've certainly seen soft form which is very good for grafts, vascular grafts. We've seen it extruded from skin, the same thing with other filling materials.

So I'm very interested in seeing any histology in humans in the skin and I would ask later on if you can provide some of that to us because I really would like to know more about the mechanism of action of this produce. Do you have anything that you could share at this time?

DR. BASTA: The significant volume of the histology work that we have done has been across multiple species but in our pre-clinical studies and so we have done intradermal, subdermal histology that we mimic applications such as those that are being reviewed today in rabbits, guinea pigs, midipigs, canine models, a variety of animal models both short term and longer term studies. That material has been submitted to the Agency. If you would like to see that imaging, I certainly can pull some of that up.

But in fact, we do see consistency across species because of the rigor of that work and some of the difficulty if you were injected a nasolabial fold taking a significant biopsy sample from a patient's nasolabial fold and the potential for an unappealing aesthetics outcome and so we have not done

significant intradermal histology or subdermal histology in dermal filler applications in the face.

We have human histology available from our vocal fold application. In fact, the first patient treated with Radiesse in the United States in the vocal fold application was a patient who had terminal cancer and had also had an injury to her vocal folds. So the physician treated her. She had donated her larynx to that physician. Several months later, she had passed away due to her underlying cancer and other medical conditions, but we have histology in the vocal fold from that application.

It doesn't answer your question, however, which is intradermal histology in humans. The best such data actually does come from the peer-reviewed literature from work that one of your colleagues did independently with this material where he had injected it behind the ear.

MEMBER NEWBURGER: In three patients.

DR. BASTA: And had a biopsy. A very limited number of patients, but that study was done independent of us. Our work has been in our

preclinical models and we have extensive data that consistently shows the same histologic patterns. We would be happy to show that to you.

MEMBER NEWBURGER: Had you not considered planting some in the volar forearm intradermal location at the same time that the patients were having this injected in their faces just to follow what's happening there. That's not a cosmetically significant area.

DR. BASTA: That's an excellent suggestion for a possible future study. It did not come up at all in the consideration of these clinical study designs and partly because we had done so many preclinical studies and had seen histology so consistently across multiple species that we were confident we knew what was happening with the material. Our gel would degrade over a period of several months. We would have collagen integration. Over time, the particles would degrade. We had a relative level of comfort from the multiple studies that had been and the rigor with which that evaluation had been done.

Your suggestion is excellent and had we thought of it three years ago we would have probably included it in one of these studies. But it didn't come up.

MEMBER NEWBURGER: Thank you. By the way, there is a definition of what a nodule is which is a solid mass that is one centimeter or larger. Anything smaller than that we'd consider a papule and that's the definition of it for dermatologist who have a Lexicon for these terms.

CHAIRMAN LoCICERO: Thank you. Dr. Munk.

CONSUMER REP. MUNK: Yes, I would like to ask the company why they are seeking the indication for HIV.

DR. BASTA: It is -- There is a two-fold thought process behind seeking this indication. One is that it has been reported to us by a number of physicians who have used this material in this indication that there is a compelling need for an agent for HIV lipoatrophy that provides immediate correction for these patients, provides superior ease of use to other materials that are available which

are currently difficult for many practitioners to use and provides an excellent safety profile and so part of our social obligation as an organization is to serve communities that can be benefitted by our therapies and when we learn from physicians that they were using Radiesse for HIV lipoatrophy treatment we quickly started work to identify how would we design a clinical study for this indication and be able to provide best practices to physicians and guidance on how best to use this material to serve the patient needs.

The other dynamic is that it is a commercial marketplace that has an interest. It is a commercial marketplace where we believe significant volumes of the material would be used and as a commercial enterprise we undertake this with the recognition that there is economic benefit in it. The market candidly is much smaller than the market in terms of dollar size than the market for aesthetics indications.

We have obviously pursued the aesthetics indications with vigor simultaneously to pursuing the

HIV lipoatrophy indication. Both clinical studies have been conducted simultaneously. But I will tell you personally as the CEO of the organization I made the call that we were going to do this clinical study and there were discussion internally of the fact that this was a smaller market opportunity than the aesthetics opportunity, but I believe that it's the right thing to do when you have a material that is useful for a population whose lives could be transformed with this material.

It has some commercial benefit and we will end up making some commercial business out of this that will be meaningful and additive to our business, but there is also a social component of it. Part of my background early in my career in the biopharmaceutical industry, I spent six years with a company that was developing an HIV therapy. I was the project manager on that program, had personal friends among HIV advocates whom I saw die through the course of that process. The drug that we were working on ultimately was not successful at demonstrating benefit on ameliorating the condition,

but out of a personal conviction for delivering a product to this community from my own past experience and the sense that our social obligations are to deliver products to useful populations.

CONSUMER REP. MUNK: I guess I have a real challenge understanding effectiveness of this product when it's for one thing in the photographs, a lot of the photographs at twelve months did not look as good as those at six months. They to me looked marginal like some of these patients would be candidates for facial augmentation.

But I think the bigger question is the financial access. You know we heard a comment about patients who could get off of disability after they had had this procedure. If they're on disability, they're not going to be able to pay for it. We're talking about several physician visits, ultimate resorption of the material which was evident on some of the twelve month pictures, how many patients need additional touch-ups, additional visits and how accessible is that going to be. There's virtually no health insurance in this country that pays for facial

augmentation.

DR. BASTA: If the question embedded in that was how accessible is it going to be, in essence it's the question of whether or not we're going to be providing a patient accessible program. We already have developed a program that involves reduced pricing for the Radiesse material based upon income levels. It achieves a level for patients that will make this treatment much more cost effective than the only other available treatment currently approved for this indication.

The other advantage is that not only will this treatment be more financially accessible for patients, it will be financially accessible by several-fold, multiple compared to the alternatives because you can achieve benefit with a single treatment. When you provide treatment with Radiesse, the patient walks out of the office with an improvement that has an immediate aesthetic improvement without the requirement for three to six treatments as may be the case for other materials that involve also three to six payments to a

physician for the physician's time.

So there are two components in accessibility for patients. One is product cost and the other is physician reimbursement and physician compensation. We are addressing as an organization the product cost component.

The other component that makes this much more accessible for patients is the fact that an immediate treatment, an immediate benefit, after the first injection provides a life-altering change without the need to wait several months to undergo through several treatments and we have found through our experience working with HIV care providers and experience working with patients who have received this therapy that the effect really is life transforming.

CONSUMER REP. MUNK: I don't doubt that and I'm glad that you've established your program to reduce the product cost, but the physician visits concern me that there will be a requirement for multiple visits and you really haven't provide much information on the durability effect and as I say

some of the photographs show a regression at the twelve month photos and I just wonder how much, at what time point these people will want to have an additional treatment.

DR. BASTA: Perhaps the best answer to that question would come at actually looking at the longer-term data. We do have 18-month followup data. It was not presented in the initial module because the PMA submission is through the first twelve months. We do have backup slides available of the 18-month information if that is appropriate to show in response to the question. We would be happy to do that, demonstrating that you do see 91 percent of patients still showing improvement at 18 months which is twelve months after their touch-up injection and Dr. Silvers can walk through that information as well.

CONSUMER REP. MUNK: I believe it's one of our panel questions to discuss the issue of longer-term follow-ups. So I think that's the appropriate time to address it.

DR. BASTA: We can certainly go through

that. Dr. Krause, is that appropriate for us to work through that information or --

CHAIRMAN LoCICERO: Well, Mr. Melkerson, this is data that wasn't presented. Should we have that at some point?

MR. MELKERSON: Data that's not presented as part of the PMA should not be under consideration here. We can take under advisement if there's a concern with longer-term follow-up and one other point in terms of cost, that's not the purview of the FDA, but we'll take it under advisement.

CHAIRMAN LoCICERO: Other questions? Dr. Blumenstein.

DR. SILVERS: Excuse me, sir. Sorry. I just wanted to address the photographs that have been put up. I just wanted to show you quickly some of the photographs that we have from the 18 months. Here's a patient that did injection and that 18-month picture was prior to any injection at 18 months and I do agree with you. I think patients do lose some product.

But the difference, patients have a

dramatic improvement at twelve months and 18 months and I always tell patients when they come in my office, they walk in the door and they say, "Inject my temples and inject here." They want everywhere and I tell them, "Look. I just want you to look sick. I want to inject those deep pits that you have in the mid part of your face. This is what's not natural. No one is going to look at the sides of your temples and say `Boy, what's wrong with you?" I try to control cost that way and I know a lot of doctors are different than I am and I see a lot of these patients.

To be honest with you, I would treat them for nothing when a lot of these patients come in and they're able to bring product to my office and the companies provide, which I know BioForm is going to be able to do that, the nominal fee that these patients pay and it's an honor to be able to treat them and I certainly hope other physicians will be able to do that. But if I can get them in to see me, I'm more than happy to help them and I know there are many other doctors in the area that are able to do

that.

CHAIRMAN LoCICERO: We're getting off course now.

DR. SILVERS: Sorry.

CHAIRMAN LoCICERO: So let's move on.

DR. SILVERS: Okay.

CONSUMER REP. MUNK: Yes, if you could quickly pull up the picture of the woman that you said was a lecturer.

DR. SILVERS: Right. Okay.

CHAIRMAN LoCICERO: Let's get Dr. Blumenstein while we're waiting for that picture.

MEMBER BLUMENSTEIN: For once, I don't have a great deal of statistical issues. But I guess this is a statistical issue in one sense. There's a long list, not particularly long, but a list of exclusion criteria that applied to the protocol, for example, the prior silicon injections, facial tissue augmentation, others, collagen, grafting, so on, collagen within the past six months, over-the-counter wrinkle products and history of keloid formation. These exclusion criteria define the patient

population from which the data were derived.

So when we come to the point of considering the applicability of this to a more general population, I'm curious about whether those exclusions were based on just a prior knowledge of the avoidance of this or whether there is data that actually shows that these exclusions are applicable or whether there's data that you've developed since or whatever. For example, with the history of keloid formation, what happens when this product is injected into a patient who has a history of keloid formation?

DR. BASTA: The simple answer to that question is we excluded those patients from our clinical studies. So your question is almost rhetorical and we do not have that information of what happens in that population.

MEMBER BLUMENSTEIN: Okay, and that's true for the other exclusions as well. I mean there's, for example, silicone injections. There's not been -- You don't have data on what happens when -

DR. BASTA: Not from any good, well-

controlled clinical studies that would provide meaningful data for review by FDA and so in the context of the design of these studies given that these were populations that we excluded precisely your observation is correct that we therefore don't have the information on what happens in a patient who has propensity for keloid formation or others of the exclusion criteria.

CHAIRMAN LoCICERO: So, Dr. Blumenstein, I guess what you're really saying is that -- Your question is will the sponsor accept those restrictions if this was approvable.

MEMBER BLUMENSTEIN: Yes, it makes for an interesting labeling.

CHAIRMAN LoCICERO: Any other questions? Okay. Let's do the photo.

CONSUMER REP. MUNK: Yes, my point here is simply that at month twelve this is somebody who I could easily see presenting for facial augmentation.

DR. SILVERS: And I'm not denying that she probably does need some, but I think the difference between her baseline and her twelve month

is still dramatic.

CHAIRMAN LoCICERO: Thank you. Ms. Whittington.

CONSUMER REP. WHITTINGTON: I would echo the concern about the potential, to me, appearance that this is an ongoing therapy not a treatment that is managed easily. While your data, I think, in one of your slides you presented this morning indicated 89 percent of the patients had to have re-injections at six months. Your followup at twelve months is from the initial injection. So that's six months later and we have nothing beyond that. So it seems to me it's more like a four to six month touch-up situation that you've presented in your initial data.

Also you indicated that some of your patients have a very firm feel to their faces after these injections and I wonder how much of that is not only collagen but other scar tissue forming as you have repeated injections again to the same area or to various planes because it appear that where you have injections initially at one plane, the next injection seemed to be at the plane below that and how much of

that is going to firm up to the point that you have distortion of the facial image after time, so I think again reiterating the need for longer-term follow-up in these patients.

My last question or statement would be in terms of your patient satisfaction you gave the patient a simple yes or no. Most all studies in satisfaction are done on Leichert scales to give the patient the opportunity to truly grade their perception of the quality of the treatment and the impact on their lives and I strongly suggest that any kind of patient satisfaction question you have be a Leichert scale and not a simple yes or no because that's just not an adequate response.

DR. SILVERS: I'm going to work my way backwards. Yes, we did do the yes or no scale and being in the office as the clinician some of the other responses I got was about 30 thank you cards, flowers, people offered to clean my office and the hugs and so again, I got to see that other side of how wonderful and grateful and how well that they did do. But we do understand that. As far as the

follow-up, we do have again the 18-month behind you.

CHAIRMAN LoCICERO: Again, this is not part of the PMA discussion, so let's leave that out.

DR. SILVERS: Sorry. Could you -- Sorry. Could you just repeat part of that first question that you had then?

CONSUMER REP. WHITTINGTON: It appears that this is an intermittent treatment not a long-lasting treatment because I think from your side specifically I jotted down an 89 percent re-injection rate at six months and that's from the initial and then again at twelve months. So it's an intermittent treatment, more of a come and go.

DR. SILVERS: As Dr. Carruthers mentioned, there's a two-fold answer to this question. First of all, the six-month injection, the volume that we injected was much less and touching, we have an opportunity to take these patients that have these devastating looks to them and to offer than essentially a free treatment and we wanted to do as much as we possibly could for them.

The touch-up injections at six months,

again since they were a much lower volume than what we gave them initially, the twelve-month follow-up still looking excellent indicates that a lot of the volume that was injected at baseline though not all still did remain. So though not all the material is lasting for a full year, we do at least show evidence that a good percentage of it and it seems on the study that about 75 percent of that material is staying for about a full year.

CONSUMER REP. WHITTINGTON: All right. Thank you.

CHAIRMAN LoCICERO: Thank you. Dr. Bartoo.

INDUSTRY REP. BARTOO: Thank you. It's always being the last of such a distinguished panel with all their excellent questions. So I only have one question. It has to do with the Global Aesthetic Improvement Scale which is your primary endpoint. Can you address more in terms of how that assessment was made? Was it the same reviewer who looked at it through all the different time points? Was it the investigator or was it an independent person who made

that assessment?

DR. SILVERS: Yes, it was the same. It was, in my practice and in all of the other sites, the same reviewer. So I would assess the patient initially, grading them as to Grade 2, 3, or 4 and then I would grade them in each visit as to the GAIS scale if they were very much improved, etc.

INDUSTRY REP. BARTOO: Okay, and did you do any sort of inter-reader studies between the investigators to either like look cross-looking at other pictures to know that you graded them in the same way?

DR. SILVERS: We did not.

INDUSTRY REP. BARTOO: Okay. That's all I have.

CHAIRMAN LoCICERO: Thank you. It's time to move on to the FDA presentation.

(Pause.)

DR. LERNER: There are passwords to guess, mine. So we're ready. Good morning. Dr. LoCicero, Dr. Krause, Members of the Panel, invited guests, ladies and gentlemen, today it's my pleasure

to present my fourth and fifth PMAs to this Panel. I am Dr. Herb Lerner, a Medical Officer in the Division of General, Restorative and Neurologic Devices and Lead Reviewer of these two PMAs.

Radiesse is an injectable filler indicated for correction of facial lipoatrophy in HIV positive patients. This afternoon I will be presenting the same device for another indication, filling of soft tissues, specifically nasolabial folds.

The Division's review team for this PMA included myself, Dr. Charles Durfor and Dr. Pablo Bonangelino. Additionally, the pre-clinical material was reviewed by David Kaplan from OCEL as well Laura Adam from our Office of Compliance. Contress Braxton reviewed the site inspections and Mary Ann Wollerton reviewed the labeling.

I will be making a short presentation today of the FDA's concerns regarding this PMA. You have already heard from the sponsor and the Agency has reviewed their presentation prior to this forum. I will not be reviewing in depth the clinical trial

itself. My comments will be related to the safety and effectiveness of the device and pointing out issues we feel are poignant for further discussion and I might add that all of your comments earlier this morning have hit on just about everything I intended to say.

Radiesse is a sterile, non-paragenic, flexible, semisolid cohesive implant. The device contains calcium hydroxylapatite granules in a gel of glycerine, water and sodium carboxymethylcellulose (PH). As you know the particle sizes are from 25 to 45 microns.

As was detailed by the sponsor, this was an open-label, multi-center, nonrandomized, noncomparative study to assess the safety and effectiveness of Radiesse for soft tissue augmentation for the treatment of facial lipoatrophy. Specific inclusion criteria included that the patient must be HIV positive, have been receiving HAART therapy for at least three years, Grade 2 to 4 on the five point Facial Lipoatrophy Scale, have a CD count greater than 250 and a viral load less than or

equal to 5,000 copies.

Patients were treated at baseline with repeat injections permitted at one month. At six month, another injection was permitted if needed. Eighty-five percent of the patients received a touch-up at one month and 90 percent at six.

The primary effectiveness endpoint of the study was to evaluate the correction of HIV associated facial lipoatrophy three months after the final treatment by comparing changes from the baseline on the Global Aesthetic Improvement Scale with confirmation using standard photography.

The secondary effectiveness endpoint of the study are to evaluate the correction of HIV associated facial lipoatrophy six months after the final treatment again by comparing the GAIS scale with confirmatory photography. The safety endpoint of the study is to record the incidence, severity and duration of all local and systematic adverse events through twelve months.

As you can see on this slide, the majority of patients were males about 48 years old

and almost half "persons of color." In previous wrinkle-filler presentations to this panel, racial data was important in determining the appropriate patient populations for which the devices were indicated. In this submission, 43 percent of the patients are African American or Hispanic. Please keep this data in mind since this afternoon I will be referring again to these numbers in my presentation.

This slide is presented to better outline the skin color characteristics of the enrolled patients. Fitzpatrick 1 patients are very fair skinned and who burn easily in sunlight. Grade 6 patients are very dark skinned and do not burn. You can see the almost equal distribution throughout the protocol with very few Type 1 patients.

As outlined earlier, the primary endpoint was the change in the GAIS score at three months. The GAIS scores, that is those scores of the assessment of improvement, demonstrated that the patients felt "much improved" or "very much improved" at both three and six months. At three months, 26 percent of the patients were very much improved and

72 percent much improved. At six months, there was still seven percent very much improved and 85 percent improved. At no time point were there any patients who rated their GAIS score as no change or worse.

I have on the screen a representative series of photographs which demonstrate that the device provides long-lasting benefit. At twelve months, facial fullness still has not returned to baseline.

This is supported by the measurements of skin thickness. A mean change at three months was 2.6 millimeters for the left cheek and 3.1 millimeters for the right cheek. At six months, this was 2.4 and 2.7 millimeters respectively. At twelve months, the values were 2.2 and 2.5 millimeters. All of these changes were statistically significant.

The sponsor has presented a series of photographs of patients treated with this device and the Agency has had the opportunity to review each of the photos and compare them to the skin thickness measurements. Correlation of these measurements with the photographs demonstrated the effectiveness of the

device at each of these time points.

I also noted in my review of the data that patients who did not receive any touch-up treatments at three or six months still had skin thickness measurements above baseline at twelve months.

It should be noted that in a listing of facial thickness I just presented and in the table of volume of radius injected there is a majority of patients having correction both at one and six months past initial injection, that the amount of material injected was quite variable between patients. From this data, it appears that the duration of effect is predictably just a few short months even though the material is considered a long-lasting implant. You will be asked a question about the device and its duration of effect after panel discussions.

The adverse events reported most commonly during the clinical trial were eccymosis, edema, erythema, pain and pruritus, all commonly seen at or around the time of any injection procedure.

The highlighted columns demonstrate there

were no events when no injections were given. All of these events generally were of short duration with some lasting about two weeks. None of these five adverse events again were reported when there was no injection. A majority of the events were determined to be mild with the remaining either moderate or severe.

There were two patients deaths during the course of this study. Both patients were available for the three month efficacy endpoint but did not have the twelve month evaluation. The deaths were not related to either the device or the procedure. One patient died as a result of their underlying disease. The other patient died as a result of suspected, unnatural causes.

One of the issues we would like to discuss with you is the list of "other device related adverse events" reported by the sponsor. Many of these were noted to be contour deficiencies, contour irregularities, deformities or lumpiness. All of these were considered by the sponsor to be device related but an expected side effect of the injection

procedure of this material.

There were no histology or x-ray studies performed and most of these resolved with a touch-up injection. Case report forms were not designed to specifically capture more information on these nodules. Patients did not report any unhappiness with these events and there was no further adverse events associated with these other reported incidences.

A non parametric test was performed to test the patient's CD4 count and whether or not they experienced the severe or moderate intensity adverse event over the course of the study. The analysis showed no significant difference in CD4 counts between the patients that experienced a severe or moderate adverse event and those that did not. It was concluded by the sponsor that the occurrence of a moderate or severe intensity adverse event was not influenced by CD4 counts.

The Agency was also concerned that this device, calcium hydroxylapatite could affect the interpretation of radiographic studies of the face or

could mimic a tumor in the soft tissue of the face. The sponsor was asked to provide a series of radiographs, both x-ray and CT, of patients at several time points during the study to assess these issues. You have already seen this x-ray and there's been a detailed discussion about this already.

These are the sponsor's conclusions from the x-ray study and I think it's already been addressed.

In summary, the Agency has reviewed the materials submitted by the sponsor in support of the use of Radiesse for this patient population. Taken as a whole, that is comparing photographic evidence with facial skin thickness measurement. It appears that the sponsor has demonstrated that the device is effective at the three month time point which was the primary effectiveness endpoint of the study. There was also evidence of the effectiveness at six and twelve months.

As for the safety data presented in the PMA, the Agency is concerned that the nodules were not better identified. The remainder of the safety

data are consistent with other fillers and it appears the device is safe for this indication. The Agency also feels that the radiographic data is sufficient to rule out x-ray misdiagnosis as we have outlined earlier. Thank you.

CHAIRMAN LoCICERO: Does anyone on the panel have questions for the FDA on their presentation? Dr. Newberger.

MEMBER NEWBURGER: Dr. Lerner, with other fillers that we have reviewed with just one notable exception, we have had human histology. Could you comment about its absence in this one, in this PMA?

DR. LERNER: Dr. Newberger, my only comment to that would be that I did not see nor did we seek more histology than we had in the pre-clinical submissions. This was reviewed by our team of biologists, histologists, etc. and they didn't raise any flags that would have asked us to consider as you suggested, you know, implantation elsewhere than the face. We didn't have those red flags.

MEMBER NEWBURGER: I recognize this was before your tenure.

DR. LERNER: Right.

MEMBER NEWBURGER: I was just wondering if you knew. Thank you.

CHAIRMAN LoCICERO: Yes, Dr. Li.

MEMBER LI: I just have an operational question. Perhaps Dr. Blumenstein could comment also. If I understand it right, this is described as a three center trial, but really it was two. I guess six were done in the third one. In the other two centers, I assume again it was single physicians in each center. Those are listed and those are the same physicians then that not only noted the adverse events but their severity. So it's obviously completely unblinded.

And I don't mean to impugn your integrity or anything, but you're the one who is doing these sponsorship, but you're also charged with potentially for instance rating a side effect or an adverse effect as mild or severe. So how do you handle that? Or how do you consider that? Or do you just take it as a fact of life and we just have to kind of deal with it as it is.

DR. LERNER: Are you asking me?

MEMBER LEWIS: Do you want one of the clinical investigators to answer that question or the sponsor?

CHAIRMAN LoCICERO: Actually, this should be the FDA section.

MEMBER LEWIS: Okay.

CHAIRMAN LoCICERO: Mr. Melkerson, is there any advice you have?

DR. LERNER: (No response.)

CHAIRMAN LoCICERO: I'll just take it as an open comment. Any other questions?

MEMBER MILLER: I have a question.

CHAIRMAN LoCICERO: Dr. Miller.

MEMBER MILLER: If I may, the material presented, that was along the lines of what was sort of requested by the FDA in terms of design. Like the issue about grading on the Global Aesthetic Improvement Scale, those grades being done by the investigator, was that a design that FDA was happy with in terms of setting it like that or following the recommendations of the FDA?

DR. LERNER: The short answer to that question is yes. The longer answer would be that as with any clinical trial or any clinical trial design, there's a learning curve and we as an agency have learned from these early trials that started four years ago or longer that some of the tools that we've put into these are no longer valid as tools that we would agree to today.

So this is what we agreed to. It may not be the best but we as an agency have also learned that anybody who comes down the pike now will not see the same kind of protocol for the newer studies. So it's a mea culpa but we didn't any better or I didn't know any better at the time.

MEMBER LEWIS: Thank you.

CHAIRMAN LoCICERO: Other questions? All right. It's time to move on to -- I'm sorry.

INDUSTRY REP. BARTOO: It's actually not a question but just a comment to Dr. Li's question. Typically in medical device trials, at least the ones I've seen, the investigators are the ones who grade the adverse events. Sometimes there's a medical

monitor involved. There's often times not a data safety committee in device trials. So what they've done in terms of classifying their adverse events I wouldn't find unusual.

MEMBER LI: I guess, perhaps, I missed it the panel pack, but typically in those cases, I agree with you, but typically there's generally a very rigorous description of what is severe, mild and so on. I just didn't see that here.

INDUSTRY REP. BARTOO: I didn't see that either.

MEMBER LI: So it's kind of left up to these two individuals to tell us what the severity, they just kind of felt it was.

CHAIRMAN LoCICERO: Okay. Let's go ahead with the FDA questions.

DR. LERNER: Question 1, up to 14 ccs per treatment of radius is required to achieve an optimal cosmetic effect and precise placement of the material in the correct dermal plan is important. Please advise FDA whether a physician training program is indicated for those wishing to use this device, and

if so, what type of training would be appropriate.

CHAIRMAN LoCICERO: Okay. We need to ask every member of the panel, so let's begin with Dr. Miller.

MEMBER MILLER: I think that some kind of training is certainly required and how extensive, I'm not sure what to recommend. But it would seem to me that the effective use of the device is operator dependent and it must be placed in the right plane and the right amount and in order to avoid some of the complications that have been discussed.

The training may be very simple for that, but I think that some requirement for a qualified person to use this material because it's deceptively easy like all the injections. It's a deceptively easy process to stick a needle in and inject something. But the longer-lasting material and the more you place, I think the more a person doing this must know how to do it properly.

CHAIRMAN LoCICERO: Dr. Li, any comment?

MEMBER LI: Obviously, I'm not a physician, but looking at this first question, I'm a

little puzzled by it. I'm not quite. Again, maybe I just missed it that 14 cc was an optimal cosmetic effect. I'm not even sure exactly what that means or how it was determined and I guess I don't know where this comes in in the training aspect, but, you know, the physician seems to be being asked to make some assessment during the patient treatment for instance how much of the material has dissipated to try to determine if you've put too much in, do you need more, not enough, and it's not clear to me how anybody make that assessment or if there's any training to make that assessment.

I could see as the number of physicians get larger that it would be easy to decide, to perhaps even be fooled into thinking it's all gone when a substantial amount of it is actually still there and they started putting larger and larger doses in. So I'm not quite sure how that gets into the training, but there seems to be a lot of decision making by the dermatologist in this application.

CHAIRMAN LoCICERO: Dr. Leitch.

MEMBER LEITCH: I think it might -- As

far as training goes, you can always have this idea of having somebody who's done it show somebody else. That always is hard to do on large scale when something's approved and a lot of people want to do it simultaneously to get that training done. So I would think perhaps a video which actually demonstrates patients where the physician does go through the decision making of, based on this amount of defect, I think this much should be used and film the injections being done in the patient and when the physician decides to stop the injection and feels that they have enough and if they massage, how that's done and these sorts of things where --

And that's often very effective because if the video covers some of these things that we've talked about, then a physician who is used to doing, all physicians, well, a lot of physicians do injections of some type, I mean, local anesthetic injections, I mean that would be another thing. It was mentioned some people use local anesthetic with this. Some do not. How is the best way to do that so that you don't obscure what you're trying, the

defect you're trying to fill, and that sort of thing.

So I think that type of an educational program would be good to have available and could be put on a website and people could do it and then print out a certificate if they went through the process that demonstrated they did it and have that as a verification of training.

CHAIRMAN LoCICERO: Dr. Newberger.

MEMBER NEWBURGER: I'm still coming back to the same problem I'm having without characterization of the human histologic response. I think it's very difficult to be able to assess, how can you train for optimal correction and what would be the persistence of that correction?

But this product has been promoted and there's been training at our dermatology national meetings for a couple of years and the technique actually, I think, is very effective. The technique that is being proposed by the company is certainly different than the technique with any other filler. That is the very fine retrograde, droplet-threading technique and the way the company has been

demonstrating this at our dermatology national meetings is to have a device which is like a clear-sided sausage casings filled with a viscous gel and then the dermatologist is given an injectable syringe and you can watch how you're dropping off these little droplets as you pull retrograde in.

That was certainly very effective and I think that should be part of the training program in addition to the video. But the company is aware of that and, as I say, it's a couple years now that I've seen it.

CHAIRMAN LoCICERO: Dr. Munk.

CONSUMER REP. MUNK: (No response.)

CHAIRMAN LoCICERO: Dr. Blumenstein.

MEMBER BLUMENSTEIN: I think that some amount of training would define the scope of the data free zone with respect to the exclusions that were in the protocol.

CHAIRMAN LoCICERO: Ms. Whittington.

CONSUMER REP. WHITTINGTON: (No response.)

CHAIRMAN LoCICERO: Dr. Bartoo.

INDUSTRY REP. BARTOO: In regards to the question, I guess the question would be is this a training where we have to show that the physicians all have certificates or something like that or is it just a patient education program that the company embarks to have it on their website, go to the conference, things like that and I have to defer to my clinical colleagues in terms of what's typical practice with other fillers, you know, whether it's already required that there is some sort of certificate training course that the doctor has to fulfill before they start using a product or what is the standard of practice.

CHAIRMAN LoCICERO: Dr. Newberger wants to comment.

MEMBER NEWBURGER: I'm not aware of any filler that has a certificate that you need prior to being able to employ it. I think though in this case if this is a product that does persist since any error is going to hang around longer, one ought have some type of certification.

CHAIRMAN LoCICERO: Dr. Olding.

MEMBER OLDING: I think we absolutely need some significant training of the physicians who are going to use this product, not because I think that they're incapable of learning or that they're slow learners, but historically we have started out with our first injectable of collagen and we build on that and this obviously is not injected the same way collagen has been injected. It's not injected the same way the other products that are available are necessarily injected and there will be more to follow it.

So as they are not all created equal, I think people need to be educated particularly that products like this one if they're injected too near the skin surface can cause problems and it's very important for people to recognize that it is in at least the subdermal, if not, the subcutaneous plane that it be injected. So I think the training required should be in the form of some sign-off whether it's sign-off having read this, you know, done this CD, or as you suggest online. But I think it's absolutely a necessary part. I do not feel that

someone has to have another physician there and train them. I don't think it's like doing a gall bladder where we saw one, did one and taught one.

CHAIRMAN LoCICERO: Dr. Lewis.

MEMBER LEWIS: I think some form of training is necessary for this. There are a number of technical details about how it's done in terms of the number of needle placements, the depth of the placement, the volume of injection, a variety of other things. All of the data has come from people who are quite expert in doing this and have spent a considerable time doing it and I think there's nothing here that would allow us to evaluate consequences of people doing it in an untutored way. So I think some sort of a -- I don't think it has to be very elaborate, but I think some training program and ideally some demonstration of understanding of that should be done with this, so that individuals using it understand the technical issues. Again, I don't think they're very complicated. I don't think it would take very long, but I think there should be an explicit training program.

CHAIRMAN LoCICERO: Good. To summarize then, a physician who uses this product will require some training, possibly with video or some other visual demonstration and possibly use of a model where the appropriate technique is evaluated and the individual is given some feedback. Does that summarize the panel's feeling? Mr. Melkerson, is this adequate response for Question one?

MR. MELKERSON: Yes.

DR. LERNER: Question two, Radiesse is composed of CaHA which is visible radiographically. The sponsor was asked to provide a better understanding of how this device will look in the skin of the face and to assess the pattern of migration of any particles of Radiesse. Provided for your review were radiographs taken at several time points to assess the possibility of this device mimicking a tumor or hiding a soft tissue tumor, as well as device migration. Please comment on the adequacy of the information to assess the risks associated with this device mimicking a tumor or hiding a soft tissue tumor after injection.

CHAIRMAN LoCICERO: Let's begin with Dr. Leitch.

MEMBER LEITCH: I think radiographically it's not a major problem in terms of mimicking a tumor. I think the point that was made that patients who have cosmetic procedures have often failed to reveal that when questioned is absolutely true. So from an educational perspective, you know, this is another issue of educating radiologists.

For example, I know if I send a patient for films who has a known history of cancer, anything that's seen the radiologist will always say might be cancer and so the patient who gets the report of that film may be distressed by having that and then insist on further evaluation which then could prompt all these other evaluations that are being mentioned. But looking at films and particularly when you have this somewhat symmetric injection, having two sides injected, it seems most radiologists would be able to ascertain that that's not a tumor.

For the plane radiographs, it just does not really seem to be a major issue and I think

people talk a lot about dental films. I think how their dental films are performed generally the material there might actually be pushed out of the way by the way the films are placed for getting the dental x-rays. So I don't think that that's a major issue or concern either.

I don't think it's clear that we have evidence from the radiograph. This is sort of embedded in this question, but not exactly stated that there's not migration of the material. I just don't think you can say that. I think this isn't like silicon where you have a pretty clear representation that you can identify on radiographs. I think this stuff is only real visible when it's clumped together and then as it becomes less -- dissipated, you know, if it gets small particles would migrate. You're just not going to be able to pick up very well by these examinations.

So I don't think you can really comment a lot about that and the films we had available to review look like that probably that streaked out pattern I was talking about may just be related to

the methodology of injection and massage immediately and perhaps if there had been radiographs that had been done, you know, say immediately after injection and then three months later before the stuff is dissipated enough so that you might be able to see does the pattern change from, you know, a week after injection versus three months where you might have had a suggestion of then migration through tissues over time, but we don't have that to look at. So I don't think we can make a comment about that. Just talk about migration relative to the radiographic evaluation.

CHAIRMAN LoCICERO: Dr. Li.

MEMBER LI: I'll defer to my surgical colleagues on this one.

CHAIRMAN LoCICERO: Dr. Miller.

MEMBER MILLER: I think the CT scan can tell you the underlying bony anatomy. I think they have been unconvincing really in terms of how obscuring this is for radiographs because the radiographs included in the packet weren't very good anyway and it's hard for me to imagine if you have a

facial fracture say right underneath that material and you just choose to evaluate with that plane x-ray or the x-rays used for that that you would obscure it. But the CT scan is conventionally done anyway on this patient, so it's maybe a moot point. But this radiopaque material overlying something you want to see on an x-ray it's going to obscure it.

I mean as far as a tumor presence, I think it may not be confusing on an x-ray. But I still think that the tissue quality after this injection is going to be different than normal tissue and it will be more firm, fibrotic, scar-like area which may be confusing in some patients in terms of what that area is and may be obscuring, but I don't think radiographically it should be problem.

CHAIRMAN LoCICERO: Thank you. Dr. Lewis.

MEMBER LEWIS: I have two or three different comments. I think, actually, I think Dr. Newberger raised some excellent points about the dental x-rays since dental x-ray technique is more similar to conventional x-ray than it is CT, my

assumption is that the fact that this material doesn't really image very intensely on conventional x-ray it would also apply to dental x-rays and that they probably would not be a problem.

On the other hand, some of the densities on dental x-rays such as she raised about periapical disease are relatively subtle and I think the failure to provide any examples of that are slightly concerning because this material will certainly overlie the apex of the upper teeth in many of these patients and it seems to me there would be superimposition of the shadows there that would not be separable the way it is with CT scanning. So I think that's actually a very valid question that has not been answered.

The second thing is I thought the evaluator's comments were slightly misleading about the question of could mimic a tumor or hide a soft tissue tumor in regard to this. It seems to me the answer to that is clearly yes if the question is is it a soft tissue tumor in the cheek at that area.

The assessment and the fact that it

becomes a relatively minor issue comes from other factors. It comes from the fact that the densities would be appear bilaterally. That you would perhaps be able to get a history from the patient in most cases about what's going on. So the radiologic image would not be the be-all and end-all of the assessment. You would have a lot of other information you could put together in terms of assessing the thing.

But the pure question of if all you were looking at was a CT image of cheek and you saw a calcium density there, without knowing more about it, I don't think you could say much about it. So the answer to the question is could it obscure a soft tissue tumor. The answer to that is yes.

And I think the assessment that was provided of saying virtually all the time no is not true. The no answer comes because of all the other factors that got into it, not just from looking at the x-ray image and I didn't think that was entirely straightforward. So it doesn't appear to me that this is a risky material and that there hasn't been

any indication of either insighting tumors or this is not an area where tumors are common, so it's not a major risk in the use of the product. But I didn't think the way the question was answered in terms of answering this question was totally straightforward.

CHAIRMAN LoCICERO: Thank you. Dr. Olding.

MEMBER OLDING: I essentially agree with everything Dr. Lewis said except with the dental x-rays. I had one recently and in fact, I think most of the soft tissue of the face is pushed out of the way when you get those bite blocks, at least when I had mine.

But I would agree that in fact they have not demonstrated whether or not this migrates or doesn't. I don't think an x-ray has demonstrated that. Whether or not, that makes any difference is another question, but I don't think they've really demonstrated that, particularly when they've said they have their patients massage the material to spread it out evenly. Those seem to be two counter, intuitive things.

As far as detection of tumor, I think it highly unlikely that they will, that the material will, actually cover a tumor in point of fact. However, I would also agree again with Dr. Lewis that they have not proven. In fact, it seems logical that they have shown that it can cover up a tumor.

CHAIRMAN LoCICERO: Dr. Bartoo.

INDUSTRY REP. BARTOO: The only comment I would have is that in their radiological study they didn't actually have any cases of soft tumor that they actually tried or even just inserted into the set to see what the doctors would say. So through evaluation or assessment you can kind of think maybe that it wouldn't obscure a soft tissue tumor, but there really wasn't any information that directly showed that they wouldn't obscure it.

CHAIRMAN LoCICERO: Ms. Whittington.

CONSUMER REP. WHITTINGTON: I don't have anything to add about the physician side, but I think that there needs to be a patient education side so that when the patient receives this device that they are given information to let their dentists know, to

let if they have chronic sinus issues and they're having sinus x-rays or other types or they have a baseball in the face, that they relay that to the physician. The patient needs to be responsible for some of that as well.

CHAIRMAN LoCICERO: Dr. Blumenstein.

MEMBER BLUMENSTEIN: No comment.

CHAIRMAN LoCICERO: Dr. Munk.

CONSUMER REP. MUNK: Yes, I concur with the comments about having the patients be educated to inform practitioners that they have had these facial implants any time they may receive x-rays or CT scans of the area.

CHAIRMAN LoCICERO: Dr. Newberger.

MEMBER NEWBURGER: I agree with the majority of my colleagues' comments. I don't feel that there's enough rigor in how the questions were posed to the radiographic evaluators to really answer this question and I don't think that there is enough information to define whether or not the device migrates.

CHAIRMAN LoCICERO: Dr. Olding wanted to

comment.

MEMBER OLDING: Yes, I just wanted to comment on, I think, Ms. Whittington's and Dr. Munk's comments. They did have in this packet a packet of information that said what other things that I suspect meant to be given to the patient, "What other things do I need to know: the microspheres and radius can be seen in x-rays." There is not a high risk that it should cause concern as long as your doctor knows about it. So they have done, they have addressed that. Whether or not that's to your satisfaction is another question, but they have addressed that in the packet.

CHAIRMAN LoCICERO: So to summarize, the panel's feelings, there are some potential significant issues with x-rays but that it's important in context that this device can be distinguished from tumor or other issues. So this would need to be made aware. The patient would need to inform a physician or the physician needs to be aware concerning this product, whatever mechanism is required. Any additional comments? Dr. Li.

MEMBER LI: Yes, Just to tack onto that. The first part of that question had to do with migration and I think we answered the tumor part adequately. But I agree with the others that we really have no idea what the migration patterns are of this device, if any, but it just seems like there's some point where you can see it and then over time you can't see it anymore. But I think even the sponsors have said even at that point there's likely to be material at least where you put it. So we have really no idea about the migration patterns of this material.

CHAIRMAN LoCICERO: So it would be -- We can just say that migration is unknown.

MEMBER MILLER: Okay. Maybe just one more comment too. I think that this material -- There are tumors that occur in the face that are fibrotic. There are sarcomas. There are all kinds of little things that occur in the face and in the context of the lipoatrophy patient where they are getting bilateral injections in specific areas consistent with lipoatrophy and all that history like

it's been mentioned, that would probably reduce the confusion caused by this material.

But in the likelihood that this material will used beyond lipoatrophy patients, it would be a little bit misleading to say that there's no confusion caused by the material without being very specific about those other qualifications. Because if you inject this on one side of the face in the patient with some sort of unilateral facial atrophy or something, this could be very confusing, what this material is.

CHAIRMAN LoCICERO: Dr. Leitch.

MEMBER LEITCH: And I would maybe make the comment beyond if it were injected some other place in the body. I mean while you can have tumors on the face that would be much less common than say getting a tumor in the breast for example. So if one were thinking about injecting in the breast to do any contouring then that's a different thing because there's more probably of having a problem there and the plane x-ray is the way that that's most commonly evaluated for screening. So if you start getting

usage which is not being asked for in this context, then it becomes a more serious issue based on where it's injected and for the etiology for which it is injected.

CHAIRMAN LoCICERO: So for this PMA, though, I think that it would be safe to say we don't know about migration. In terms of tumors, it's potentially confusing, may require additional radiologic evaluation and history in the context of the particular patient. Does that answer the FDA's concerns?

MR. MELKERSON: That's an adequate response. Thank you.

DR. LERNER: 21 CFR 860.7(d)(1) states that there is a reasonable assurance that the device is safe when it can be determined that the probable benefits to health from use of the device for its intended uses, when accompanied by adequate instructions for use and warnings against unsafe use, outweigh any probable risks. Considering the data in the PMA, please comment on whether there is a reasonable assurance that the device is safe.

CHAIRMAN LoCICERO: Okay. Let's begin with Dr. Munk.

CONSUMER REP. MUNK: Yes, I believe so.

CHAIRMAN LoCICERO: Dr. Blumenstein.

MEMBER BLUMENSTEIN: Conditional on a clear articulation of where data have been collected and risks are known, yes, I think so.

CHAIRMAN LoCICERO: Ms. Whittington.

CONSUMER REP. WHITTINGTON: Yes, I think so.

CHAIRMAN LoCICERO: Dr. Bartoo.

INDUSTRY REP. BARTOO: I agree.

CHAIRMAN LoCICERO: Dr. Olding.

MEMBER OLDING: I would agree that I think it's proven its effectiveness and I would just like to --

CHAIRMAN LoCICERO: Safety. We're just on safety.

MEMBER OLDING: I'm sorry. It's safety and in fact, when compared with the other materials that are out there when you can inject a product that you can get the result that you want when you inject

it as opposed to injecting it in larger volumes, it is a much safer proposition because you know where you're injecting it.

CHAIRMAN LoCICERO: Dr. Lewis.

MEMBER LEWIS: I think the answer is yes.

CHAIRMAN LoCICERO: Dr. Miller.

MEMBER MILLER: I think it's yes. I think the safety question is this dynamic question of a balance of risk and benefits and I think that the benefits for this set of patients are enormously and so the burden of really documenting what the risks are may be a little less because the benefits are so large. But you start to move outside of this set of patients and the risks, the need to demonstrate the risk profile becomes greater because the benefits start to fall off a little bit. I think it needs to be emphasized strongly that the safety is in these patients.

CHAIRMAN LoCICERO: Dr. Li.

MEMBER LI: I believe that as far as the data goes, it seems to be safe. However, I think that the data is actually somewhat lacking in how

rigorous it is. There's no human histology. We have this issue about the severity of ranking. We still have this kind of lingering question of kind of unknown importance about the nodules.

So it's really there's just kind of this absence of evidence of any problems but absence of evidence is not evidence of absence if you'll forgive me. So as far as how they've looked, I think it seems safe. But I don't think they've looked as hard as would make me completely comfortable to say it's completely safe without any question.

And I know this isn't the spot to bring it up, but it's kind of gnawing at me so I'll just mention it. The elephant in the room with us is that we know that this device is going to be used outside of this patient group. So we're kind of talking about safety. You know, the questions confine us to the safety as of the PMA, but we know in real life that's really not the case.

CHAIRMAN LoCICERO: Dr. Leitch.

MEMBER LEITCH: I agree with Dr. Miller about the benefits and risks issues and in this

particular study, the satisfaction of the patients was so high and that they would recommend it that the patients are saying what they're willing to accept in terms of the experience they had and so I think for this set of patients that it is that risk/benefit ratio for them is acceptable.

CHAIRMAN LoCICERO: Dr. Newberger.

MEMBER NEWBURGER: I agree with Dr. Li's comments. I think that this was a small number of patients without histology. I'm not comfortable and I really would have liked to have seen more rigor. So just 100 patients, that doesn't really give me that much confidence frankly.

Because the product has been used off-label, I went online to the FDA website and got adverse event reports off the MAUDE system and there are 45 that are there, some of which are allergic, some of which report responses like tissue necrosis. Now these are not patients' complaints which are characterized in terms of HIV lipoatrophy, but I'm just saying that I think that we need to have a little more information before we can be real

comfortable about the safety. This is on the FDA website.

CHAIRMAN LoCICERO: Okay. To summarize, within the limits of this study and for this PMA, the panel feels that it is safe with qualification, that it's a small study, limited group, well studied in these particular patients, but that beyond that we really don't know. Does this satisfy the FDA?

MR. MELKERSON: It's an adequate response. Thank you.

DR. LERNER: 21 CFR 860(e)(1) states that there is a reasonable assurance that a device is effective when it can be determined, based on valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will produce clinically significant results. Considering the data in the PMA, is there reasonable assurance that the device is effective?

CHAIRMAN LoCICERO: Okay. Before we begin asking questions again, it's for this PMA for

this indication. Dr. Newberger. Would you like some time?

MEMBER NEWBURGER: Yes, I would.

CHAIRMAN LoCICERO: All right. Let's begin with Dr. Lewis.

MEMBER LEWIS: I would say the answer is yes. The time course of the effectiveness has not really been addressed in terms of deterioration and effectiveness. But for immediate use, I think the effectiveness is proven.

CHAIRMAN LoCICERO: Dr. Olding.

MEMBER OLDING: I believe it's effective.

CHAIRMAN LoCICERO: Dr. Bartoo.

INDUSTRY REP. BARTOO: I agree.

CHAIRMAN LoCICERO: Ms. Whittington.

CONSUMER REP. WHITTINGTON: I would also echo that I think it's been shown to be effective for potentially short periods of time not -- The length of effectiveness needs to be included.

CHAIRMAN LoCICERO: Dr. Blumenstein.

MEMBER BLUMENSTEIN: I agree with the previous commentors that it is effective and that the

duration of effectiveness has not been adequately studied and that I would emphasize that the scope of the effectiveness is quite limited because of the type of study that was done.

CHAIRMAN LoCICERO: Dr. Munk.

CONSUMER REP. MUNK: I agree with the previous comments.

CHAIRMAN LoCICERO: Dr. Newberger.

MEMBER NEWBURGER: Back to me. I'm still having trouble formulating, expressing, my concern. I think it's effective for a short period of time. Yes.

CHAIRMAN LoCICERO: Dr. Leitch.

MEMBER LEITCH: I think it's effective. It seems it's effective at least for six months and for some patients moderately so to twelve months and I think it would be beneficial, you know, this additional study that's being planned. I think that's a good thing to help clarify further.

CHAIRMAN LoCICERO: Dr. Li.

MEMBER LI: I'm in agreement with the previous comments.

CHAIRMAN LoCICERO: Mr. Melkerson, I think we have relatively good consensus here that the product is effective. Wait. I didn't get Dr. Miller. Sorry.

MEMBER MILLER: Can I play too? I think it's effective and I think the length, it's not forever but it's as good or better than anything else that's been used for this. So I would say it's effective.

CHAIRMAN LoCICERO: Good summary, I think. Mr. Melkerson, is this an adequate response?

MR. MELKERSON: Yes, it is. Thank you.

DR. LERNER: The sponsor has provided twelve month data to support the safety and effectiveness of their device. Adverse events were few and generally minor. The device itself, CaHA, is intended as a long-term implant. Based on the data provided, and the length of follow-up in the clinical trial, do you feel that a post-approval study is indicated to assess further long-term safety or effectiveness issues?

CHAIRMAN LoCICERO: Okay, again, with

qualification, we know that the sponsor has 18 month data that's not being presented today and with that qualification, Dr. Olding.

MEMBER OLDING: The value in HIV positive patients is a relatively long-lasting product and unfortunately, we haven't seen that from this particular set of data that was presented and, however, having said that, anything that lasts a year is certainly going to be beneficial to that patient population. There are other things that are much shorter lasting, not necessarily volume materials. But I believe that an 18 month follow-up trial would be very appropriate and necessary.

CHAIRMAN LoCICERO: Dr. Lewis.

MEMBER LEWIS: I'm a little unclear about the question. I gather that the material is not really being marketed as a five year solution, but as an immediate solution and nowhere in here have I seen the question of what length of effectiveness is being stated or advertised or however you want to phrase it.

So I guess in answering this question,

I'm not sure what it addresses. If the question is is this a device which works for its intended purpose for approximately a year, I think that's been answered. If we don't need any further information, then no follow-up studies would appear to be necessary to me.

If the question is do we really want to know more about it in terms of how long it lasts and what happens to it, then the answer is yes, follow-up studies are needed.

So your question is not clear to me in terms of what you're seeking and it really depends on what you want. If you simply want to answer the question, does the product work and is it safe with a one-year window, the answer to that seems to be answered and no further studies would be necessary. But if you -- I don't think the question has been answered very well as it's been stated by multiple people here about what really happens to this over time and what the long-term state of the histology is. Those questions all would be nice to know but they're not essential in the marketing of the product

for its apparent purpose.

CHAIRMAN LoCICERO: Dr. Miller.

MEMBER MILLER: I agree I think with Dr. Lewis. I think the efficacy and the safety in this patient population has been adequately demonstrated by what's been shown to us and further studies are not required for that issue.

CHAIRMAN LoCICERO: Dr. Li.

MEMBER LI: I agree with Dr. Lewis.

CHAIRMAN LoCICERO: Dr. Leitch.

MEMBER LEITCH: I think longer-term studies would be helpful to address some of the concerns, you know, how often does it happen that because of the texture of the cheek that prompts somebody to do a biopsy or seek further evaluation, the issues of does anything happen to the patient subsequently that would suggest a migration problem. I think those are sort of the long term things.

Again the marketing point, if it's not stated to last longer than what has been demonstrated so far, then if the patients are properly informed about what to expect, then they know that it's not a

lifetime product and they're going to have to have other injections, I think that's acceptable. But when you have questions raised, if it turns out nobody ever has to have further evaluations for concerns of tumors or these sorts of things, then it's more reassuring that that's not a major issue.

CHAIRMAN LoCICERO: Dr. Newberger.

MEMBER NEWBURGER: Since everyone is getting topped off at one month and again at three, no sorry, six months, I don't see the value of doing a post-approval study because I don't see this as a long-term implant.

CHAIRMAN LoCICERO: Dr. Munk.

CONSUMER REP. MUNK: Yes, I think there are a lot of questions that might be addressed in longer-term follow-up study particularly some of the gaps due to the exclusions in this existing trial. If this product does prove superior, then it would be helpful to know if it could be combined or used to touch up people who have used other products. And I agree with the comments about durability, but I would also just want to state that 18 months is very short

in the life span of people with HIV under current treatment.

CHAIRMAN LoCICERO: Dr. Blumenstein.

MEMBER BLUMENSTEIN: Yes, additional studies.

CHAIRMAN LoCICERO: Ms. Whittington.

CONSUMER REP. WHITTINGTON: I agree with Dr. Munk and I'd like to elaborate on that. I think certainly the treatment for HIV is much more sophisticated now and 18 months is a short period of time. I am concerned about potential migration. Also in defining some levels of the severity of the adverse events, I think, is important as they lengthen those studies or look at this product.

CHAIRMAN LoCICERO: Dr. Bartoo.

INDUSTRY REP. BARTOO: I agree with Dr. Lewis and Dr. Miller that for the indications that they're asking for and the time period as long as it's disclosed in their claims and labeling. I don't think post-approval studies are required at this time. They do have significant experience with this particular exact product in their 510(k) marketed

product. It's been on the market since 2001 worldwide.

So as Dr. Newberger said, there were about 45 AEs mentioned in the MAUDE database over five years or so is not -- Oh, in the past two years, okay. But even still, it's been on the market for quite a long time. So I would think that some of the safety concerns would have shown up at this point.

CHAIRMAN LoCICERO: Dr. Newberger.

INDUSTRY REP. BARTOO: If I could make a comment about MAUDE database reporting estimates of adverse events because it still is a voluntary reporting system on the part of the practitioner. If an event is reported to the manufacturer, the manufacturer is to report it into that system. But someone else can put it into the system themselves on a voluntary basis and we believe that it's somewhere under ten percent of adverse events that ever get that far. There's a substantial under-reporting of that.

INDUSTRY REP. BARTOO: And I understand that in Europe too it's under-reported.

MEMBER NEWBURGER: Europe is even worse.

CHAIRMAN LoCICERO: Okay. To summarize, I think, the way the panel feels about this is that it would be very desirable to have further long-term studies. Eighteen months are going to be helpful but will not answer the concerns of the panel and post-market study is not really required, but there is concern that safety and effectiveness are not durable. Does this answer the FDA's question?

MR. MELKERSON: I believe so.

CHAIRMAN LoCICERO: Okay. This concludes the questions by the FDA. The sponsor and the FDA will be making presentations this afternoon. Are there any individuals present who wish to comment in the public commentary section? With the Executive Secretary's approval, I will not read the qualifications necessary for a public discussant. So we are ready to adjourn for lunch and we'll return at 1:30 p.m., 1:15 p.m. Off the record.

(Whereupon, at 12:33 p.m., the above-entitled matter recessed to reconvene at 1:26 p.m. the same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1:26 P.M.

DR. KRAUSE: We're ready to start again. It looks like everybody is ready. Okay. Dr. LoCicero?

CHAIRMAN LoCICERO: Okay, it's time to ask the FDA if they have any further comment.

DIRECTOR MELKERSON: The FDA has none.

CHAIRMAN LoCICERO: Is there any further comment by BioForm Medical?

DR. BASTA: Just a minimal comment; first regarding the panel discussion on training. In fact, the descriptions behind many of the panel members of the desire for video-based training or DVD-based training or web-based training opportunities is something that we currently have planned as part of the preparations for launch for the facial esthetic indications and so we would be providing that training to physicians and we think the recommendations of the panel there are quite helpful in terms of defining what the needs of physicians would be. We appreciate the input in that regard. There was also a question

that was raised by several of the panel members regarding the inability to draw conclusions about migration from the radiology studies and, in fact, the radiology study was not designed to provide conclusive evidence regarding migration.

That was an accurate observation which the panel members have made in that regard. Separately, not presented today but which has been submitted to FDA as part of the preclinical package, we have conducted numerous preclinical studies but we also included in that portfolio a specific preclinical study designed to address the migration issue looking at histology in multiple tissues after injection of the material which was designed to address the question of whether or not this material would migrate, and we have not seen evidence of migration in that study, but the panel's observations were correct, that the radiology study was not adequately designed nor would CT scans be adequate to determine whether or not particles migrate. That evaluation was done separately in an analysis that has been submitted and reviewed by the FDA review panel. Thank you.