evaluators assessment of the wrinkle severity at six months after treatment and they would also measure the volume of the material injected.

Subject's and the investigator's nasolabial severity scores were compared and measured at two, four and six months.

The number of treatment sessions in order to achieve optimal cosmesis is another secondary endpoint that's been employed.

And blinded evaluator's use of the Lemperle scale at one month, at four months, and the subjects also used the Lemperle scale in their assessments were monitored at one, four and six months.

With regard to safety endpoints, safety was evaluated typically by comparing the incidence and severity of local and systemic adverse events as reported by the treating investigator from the pretreatment skin testing through six months post-optimal correction visit, or by comparing the incidence and severity of clinical events during and throughout 12 months after treatment completion.

And again, this is a summary and compilation of all of the protocols to date.

Serum samples for humoral responses were also collected in some of the protocols but not all

at one and six months post treatment.

And summary of the patient populations, the demographics ranged with regard to age. Patients were typically 30 to 77 years of age, and the mean ages ranged from 52 to 56 years. Subjects were predominantly female as discussed earlier and Caucasian. And with few exceptions, the studies enrolled low number of subjects with Fitzpatrick skin types, and that range was from 4 to 10 percent.

With regard to exclusion criteria and again the exclusion criteria will be a criteria where patients are not allowed to enroll in protocols, if there was evidence of an existing immune response against the study materials, if there was a history of bleeding disorders, connective tissue disease, pregnancy, or if a patient was unwilling to forego other facial treatment regimen, such as alpha hydroxy agents, botulinum toxin, microdermabrasion and retinoic acid therapy, during the study, they were not allowed to enroll into the study, and this is not an entire list of all of the exclusionary criteria for all of the protocols but these are a summary of a few common ones.

Most of the studies also excluded patients with current or recent soft tissue facial

augmentation, immunosuppressive therapy, chemotherapy, systemic corticosteroids, anticoagulant therapy and any use of other investigational products at the time.

With regard to the pretreatment plans, they were generally assessed and the procedures were performed within one to four weeks of initial assessment. Of course, they would have to have review of their inclusion and exclusion criteria. A physical exam was typically performed, and they also collected a medication and medical history. A baseline assessment of wrinkle severity was also done so there would be a comparative measure. And with regard to protocols which evaluated immune response, pre-baseline serum samples were collected, and then again we've discussed the frequency thereafter and the treatment plans.

With regard to the treatment plans employed and dermal filler protocols, immediately after device implantations, patients were monitored for adverse outcomes. Treating physician and subject evaluations of the cosmetic outcomes were also performed, and we discussed that as well.

After each injection session, the injection technique, we discussed those and the device volume

and anesthetic use were generally recorded and photographs were generally collected during all study visits.

With regard to short-term follow-up, in most of the studies, subjects were contacted by either telephone or evaluated at a clinic visit 72 hours after treatment in order to determine incidence, severity and type of adverse event outcomes.

Subjects were also generally completed a post-injection diary that recorded their injection site reactions during the first 14 days after their treatment. Two weeks after the initial treatment, subjects returned to the clinic for evaluation of their wrinkle severity scale and adverse events. Between one and three touch-up treatments were performed in order to achieve optimal correction.

With regard to longer follow-up, the frequency and duration of clinical varied depending on the composition of the dermal filler. So some of the protocols required follow-ups at 1 month, 3 months, 6 months and 9 months after the last injection, and then one protocol as far as to 12 months.

At these visits, incidence, severity,

duration and type of adverse events were also recorded. Product effectiveness with regard to wrinkle severity scales, global aesthetic improvement and the treating investigator and/or subject satisfaction, those areas were also monitored and determined either by a masked evaluator, treating physician and subjects as I discussed prior.

With regard to the study types of designs, there are advantages and disadvantages to many types of the protocols that were used. So with regard to within-patient controlled protocol, the advantages of using that type of protocol includes that you can remove between-patient variability, requires smaller sample size for the given statistical power, and you can eliminate the imbalance of missing data between treatment groups.

However, the disadvantages include the fact that masking may be more easily compromised since each of the subjects received both of the treatments. You can also have asymmetry if you're using to different types of devices, and you cannot decipher between the cause of systemic side effects if you're using two different types of devices.

In addition, if you use concurrently controlled protocols, the advantages include the fact

that masking can be more easily maintained and systemic side effects can be attributed to the particular device, each of the specific devices, and you also have symmetric outcomes.

However, the disadvantages include that you probably require a larger patient population. There could be an imbalance of dropouts between the control and the treatment groups, and randomization may not account for all of the population differences.

In a single arm study, when there's no control and there's no historical control, this can be appropriate when you cannot randomize to the device type. However, the weaknesses can include that you can't mask, there could be a possible bias and the demographic and prognostic factors are not necessarily comparable.

With regard to superiority versus non-inferiority testing, superiority hypothesis can be appropriate when the control is a sham, there's no treatment or the treatment is known to be ineffective at the primary analysis time point. Treatment is also, if it's an adjunct to another treatment, for example, if the device is used with another device, and the other device, is better than the subject device alone.

Single arm comparison when it's compared to baseline, that's when it's also appropriate, and also it could be appropriate when the device is an enhancement implying that there's some superior type of aspect to the treatment procedure.

Non-inferiority hypothesis can be appropriate when there is a beneficial aspect of the device over the control, and also when a control is the active device and is known to be effective at the primary analysis time point.

There are some notes on superiority testing. The margin of superiority doesn't generally appear in the hypothesis but it is used implicitly for the purpose of sample size calculation. And if a claim is specific, as to the amount of the superiority, then the hypothesis will have to include that same amount.

And with regard to non-inferior testing, the margin of the delta is actually defined as the maximum clinically insignificant difference beyond which the device would be considered clinically inferior. Also, with regard to non-inferiority testing, it is not the observed treatment difference in the study sample that must be less than the delta, but the lower limit of the 95 percent confidence

interval around the observed treatment difference.

And also, the non-inferiority hypotheses are written in such a way that rejecting the non-inferiority null hypothesis means that the non-inferiority has been met.

So again, the purpose of the presentation was to present a synopsis which characterizes the different types of protocols that have employed to date and also to address our potential statistical issues. And subsequent to this, we'll actually go into further conversation with Jiyoung about the future of evaluation of dermal fillers.

DR. DANG: Thank you, Dr. Francis. To move along, with growing consumer demand, FDA expects the continued submission of premarket applications for dermal fillers for both indications for filling of wrinkles as we have seen thus far and possibly for new indications for augmenting and contouring of the face and possibly the body.

Some of the aesthetic uses reported in the literature and public media include lip augmentation, contouring of the chin and jowl, contouring of the nose, cheek augmentation as well as hand volume augmentation and there are many others that are not included in this list and certainly each patient can

receive multiple of these types of treatments.

Injection other than for filling of wrinkles may introduce new risks due to differences in physiology of the injection region such as proximity to bone, proximity to nerves and vessels, vascular occlusion, thickness of the dermal and sub-dermal layers, tolerance to swelling, dynamic range of motion of tissue, tissue function as well as device migration. And again, this is not an exhaustive list. But certainly these are types of things one would consider would go into determining a risk benefit ratio, and they may or may not be the same or different between filling of wrinkles and dermal filler use for tissue recontouring, and certainly want to consider the risk benefit ratio when determining a clinical study design.

There exists a baseline of safety and effectiveness data that have been collected thus far from clinical studies that have been submitted to the FDA for support of premarket approval of dermal filler use for filling of wrinkles and folds. And with some of the potential new indications for use, they may or may not be differences in aesthetic considerations for effectiveness, immune response, inflammatory response and adverse events.

And these and others would play into inputs into clinical study design considerations, and some of the basics of a study design would include controls which would provide a method to study potential risks of treatment procedure, possibly independent of the study device and as well as aid in decrease of bias in the treatment.

One would also have to consider whether or not adequate controls exist, and they may not exist for all cases, and there may or may not be a need for possible use of the subject baseline as a condition of control.

Study endpoints generally include both effectiveness and safety endpoints. Effective endpoints could consider things such as aesthetic improvement, validated assessment, and also the frequency of filler injection either for optimal correction or for the maintenance of correction. And safety endpoints could consider subjects such as items that are specific to the injection site itself, the amount and frequency of the filler injected, the effects on native tissue physiology, tissue scarring that may or may not happen with the use of a device, as well as toxicity both local and systemic.

Study duration can also include

considerations such as durability of the treatment, as well as any sort of short and long-term clinical issues that may or may not affect device effectiveness and safety.

With those types of considerations of mine and many others that you may also develop, the FDA questions to the Panel carry issues such as whether or not nasolabial folds represent other parts of the face, whether it represents facial wrinkles as well as various aspects of clinical study design considerations both premarket and postmarket.

DR. LoCICERO: Thank you. I'd like to thank the FDA speakers for their presentations, would like to allow the Panel some time to ask questions of both speakers this afternoon. Are there any initial burning questions? Dr. Gooley.

DR. GOOLEY: This is for Dr. Francis. As I briefly said this morning, I was sort of struck by what I considered to be relatively small sample sizes for these studies and particularly for the studies that are designed with non-inferiority in mind, because as you know, non-inferiority trials take larger sample sizes than superiority trials. So what sorts of differences are typically looked at either for superiority or non-inferiority kind of trials and

for what endpoints in setting up these sample sizes? Or do you know?

DR. FRANCIS: Repeat the question please. Speak up some.

DR. GOOLEY: Well, I guess I'm wondering basically how are the sample sizes chosen? So what sorts of differences are assumed when the studies are designed for the sample sizes?

DR. FRANCIS: This is actually Phyllis Silverman and she is our statistician and she and I did the slides together. So she can answer this.

MS. SILVERMAN: Hi. Yes, Phyllis Silverman, FDA statistician. Generally for non-inferiority, if we have a five or six point scale, we generally feel that a half a point is a -- since a full point is generally the minimal clinically detectable difference, we usually require a half a point to be the margin of non-inferiority.

And for superiority studies, generally it's a full point.

DR. GOOLEY: Okay. And so can you really do that with 100 to 200 patients --

MS. SILVERMAN: Believe it or not, we can.

DR. GOOLEY: So you're assuming that the experimental treatment is quite a bit better than the

treatment that you're comparing it to, I guess and --

MS. SILVERMAN: Yes. We require the companies to do a sample size justification based on their primary endpoint, whether it's non-inferiority or superiority and then we use their effect size and we make sure that they'll have enough power and enough patients.

DR. GOOLEY: I'm sorry. And is there any consideration given to safety in the sample size calculations or is it based primarily on efficacy?

MS. SILVERMAN: With breast implants, yes. With wrinkle fillers, generally they're powered for efficacy.

DR. GOOLEY: Thank you.

DR. LoCICERO: Dr. Li.

DR. LI: I'm not exactly sure how to phrase this question but this goes back to my ongoing theme that these are made with very different materials that could have very different responses over different periods of time. So how -- I'm a little -- well, my question is how do those variables get affected or rolled into your trial design? Because I don't really see any mention of any material issues at all through here. So if you have one material, for instance, that perhaps degrades very quickly

versus one who doesn't degrade very quickly but there's also a particle size difference or a dose difference, how is that all taken account in there?

DR. DANG: Is the question about the presentation or --

DR. LI: Well, I didn't hear anything about that at all in the presentation. So maybe my question is it that just kind of hidden in here somehow? Is it a detail that's not directly discussed or is it just an area that wasn't addressed?

DR. LoCICERO: I think Mr. Melkerson wanted to make a comment.

MR. MELKERSON: Actually the details of the studies themselves are included in the summaries that were links in the public information and hard copied in your Panel packs, but Dr. Charles DURFOR is actually probably the lead reviewer on many of these and he could give you a more detailed answer.

DR. DURFOR: I appreciate your question. I think it's very important. Generally before a study begins, we have a sense of how long the product will last, and so we work very hard to make sure that patients, that the products have a reasonable, if it's a with-in patient study design, where a patient

actually could suffer from facial asymmetry, we try and work very hard to make sure that the products will have a similar residence time.

DR. LI: Well, I guess I'm looking for a more insidious problem. For instance, you might have Product A where you have some kind of visual assessment and that you score with some visual assessment scale, and then another product that you're also going to make a similar assessment on. Is it possible from a statistical point of view that one material just has a broader range or a larger standard deviation than the other?

DR. DURFOR: Could you be more specific on the type of visual assessment? Are you talking about a wrinkle severity?

DR. LI: Well, fine. It doesn't matter to me in my question but that would be fine. So in other words, maybe Material A spans maybe standard deviation of, for whatever reason, four or five units but another one only has spans or a range of, you know, one or two units. You know, how do you deal with that ahead of time?

DR. DURFOR: Right. And I certainly will yield to Ms. Silverman who's done a lot of the statistical analyses but from a very basic point of

view, all of the products which are used are FDA approved products and are commercially available, and so there may be times where you will have a HA product versus a collagen product, but if you're comparing FDA approved products, it's appropriate.

All of the endpoints are done with regards to the same scale, and they are usually done as a point estimate at a particular time point. So we have not run into that problem. We have not observed that problem in terms of some products offering a variation of five points versus two. Instead, what we generally try and do in these studies is make sure that the patient receives an optimal cosmetic correction, and that's when the clock starts. And that's a prespecified endpoint in terms of what the physician feels is a valid, best as you can do with the patient, and then you start the clock there.

Does that answer your question?

DR. LI: Just one more follow-up before I confuse myself some more. Did I just hear you right that you essentially use the number of units necessary to get an effective treatment? Is that what I just heard you say?

DR. DURFOR: Right. Most of the wrinkle severity scales are a five or six point scale and as

Ms. Silverman has mentioned, a point difference as this Panel has already discussed on products in the past, is usually determined pre-beginning of the trial to be whether or one point difference is or is not a clinically significant difference.

DR. LI: But that would mean then perhaps different patients would get different amounts of material to get to the same clinical endpoint?

DR. DURFOR: That's correct. And that sort of information is presented in the label. We feel it's important not only to give the consumer an idea of how many treatments some products may need, one product may need on or two treatments, one may need two or three, we try and provide that on the label for each product, as well as an idea of the distribution of amounts that go into each patient, so that the product is accurately labeled.

DR. LI: Okay.

DR. LoCICERO: Other questions for the FDA?

(No response.)

DR. LoCICERO: Thank you very much. We're scheduled for a break, but we're actually a little early. My goodness. So at this point, what we'd like to do is ask for general impressions and comments at this time, and I'm going to sort of be a

little bit in reverse this time. So, Mr. Halpin.

MR. HALPIN: So with regard to clinical study designs, my first general take away from this is that for nasolabial folds, I think it's important to note that the study designs have been iterative over time, and that manufacturers and the FDA have been able to use the prior trials in order to design better or more improved trials to achieve their goals. I think these trials are primarily designed to evaluate efficacy. They use non-inferiority as well as superiority. Endpoints sometimes are even nested with a non-inferiority primary endpoint followed by a superiority secondary endpoint.

So I think the trial designs are fairly sophisticated. They will detect differences in volumes if the two products require difference in volumes and they typically are over landmark time points, three months, six months, nine months, where they compare the two products.

In terms of endpoint analysis, most of the endpoints are validated, have been photographic scales as well as scales that are used by actual blinded live evaluation. So they're fairly sophisticated trials that are developed over time.

I think as you look to try to apply this to

new indications, I think one of the major questions will be for a first product in, what do they need to be compared to, if anything, and how do we evaluate that first product that's going through the process for a new indication beyond the nasolabial fold.

DR. LoCICERO: Ms. Rue.

MS. RUE: We talked about efficacy, but I think obviously one of the concerns we need to do as part of the outcomes is the safety, and also in listening to the discussions, obviously there's some common areas of the face that we talked about that are similar to the nasolabial folds that would be easier to roll in than some of the others, but the other areas are going to be continued to be used as sites also. We need to continue to figure out how to evaluate those.

DR. LoCICERO: Dr. Li.

DR. LI: It seems where I am at the moment, it's seems like I understand how the trials are being done now, and I understand that it's a reasonably effective way to evaluate the different products but the frustration part for me is that it's not really done in such a way that I could basically evaluate the materials because we're using different amounts perhaps over different periods of time, with

different endpoints. So although we walk away saying Device A used in such a manner evaluated at such and such an endpoint is relatively safe, it doesn't give me any basic information about that material.

So which means each time that material is used in another indication or another amount, we don't really know anymore than the time we did before. So we end up having to do the whole study over again.

So I don't know quite how to get around that. So we're kind of satisfying one question but we never really seem to get toward the basic question of evaluating essentially a dose response for a particular material in a particular location.

DR. LoCICERO: Dr. Anderson.

DR. ANDERSON: Well, I'm basically satisfied with the endpoints. I think that they are reasonable endpoints given the product and the popularity of the product.

I also think that I'll be really happy when ASPS has their patient satisfaction scale. I've advocated that for years. In the absence of that, I think we can use a patient satisfaction Likert scale as a way of indicating patient satisfaction.

With regard to new indications, I'm

wondering if there are publications or presentations that have been given at professional organization meetings that we can draw on in an effort to see how these products are being used off label and perhaps provide some guidance in that regard.

DR. LoCICERO: Dr. Gooley.

DR. GOOLEY: Well, not to beat a dead horse here, but I guess I'm still a little bit surprised at the small sample size. Now, if the assumed true differences in efficacy are relatively large, studies will be adequately powered, and I'm sure they are. I don't know what they assume true differences are, but I guess that raises a question in my mind of safety. With only 100 to 200 patients per arm, I don't know how much confidence you have that one product is safe enough or safer than another product, and that would be one concern that I would have with these reasonably small sample sizes.

DR. LoCICERO: Okay. So we've heard from our consumers and industry and our scientists, non-clinical scientist. Now, we want to move into those who are going to actually do the study. So, Dr. Walker, comments?

DR. WALKER: I think that I too am satisfied with the endpoints but the issue of off-

label use is not being addressed and absolutely needs to be evaluated. Although the nasolabial folds is a very consistent focus, perhaps adding one additional site per product may be a way to move forward. I'm not exactly sure how else to address that issue because it needs to be addressed because we are all using these products outside of the nasolabial folds routinely.

DR. LoCICERO: Dr. Burke.

DR. BURKE: I think that I'd like to see quantitative data. I mean I know that photographs are good and patient satisfaction is good but perhaps measurements could be made of dermal thickness with time. And I might even like a whole different kind of study that everyone has the same amount put into the nasolabial fold and instead of having all the variability, have a really strict protocol that X amount will be injected and will be evaluated at one month, three months and six months and we would do a real measurement of dermal thickness at a prescribed place on the patient's face. I know that there's a lot of variability with that. So you'd have to do several measurements around a point that is measured and documented with a photograph.

But I think I would like to see some

studies like that if were ever possible.

DR. LoCICERO: Dr. Newburger.

DR. NEWBURGER: I think that the algorithms used in the past have been terrific when we use these products as wrinkle fillers but generally there's been a change in the art and these products are used more to provide volume in areas where it has been lost, whether it's through disease, age or trauma or congenital deformities. And in order to do that, I think we do need data. I think we need objective and quantifiable data, and I've often heard that there is no validated scale. There are visual ways to validate scales, whether it's in photographs, looking at the maintenance of how long a fill can be demonstrated or using some of the 3-D imaging systems such as Canfield spectra.

In terms of durability extrapolating from nasolabial folds to other sites, I think that since there are different stresses towards mobility in other areas, it may not be directly applicable but I too am looking for more data to look for persistence of response durability of the effectiveness as well as safety.

DR. LoCICERO: Dr. Bigby.

DR. BIGBY: I actually have sort of general

comments that are meant more to be food for thought than actual suggestions for the discussion about the questions.

One is that, you know, since these are by and large cosmetic procedures, I think that patient reported outcomes are actually the most important and should be given the most emphasis, you know, so things like patient satisfaction and changes in quality of life, I think are actually much more important than measured scales.

The second food for thought idea is that I'm not sure that getting FDA approval for an indication is going to change use much because the patients have already sort of voted. I mean they're coming with lots of money in hand to have these procedures. So they really voted for having them, and I'm not so sure that getting approval is going to actually help the manufacturer all that much.

And then the third one was I heard the statement, I don't remember exactly who made it, about sort of you can't study the biology of these agents by doing biopsies because, you know, people won't want to have biopsies done on the face. However, you can learn a lot by doing studies on other areas and have it done on volunteers. So I

think that that's an argument that actually has no validity.

DR. LoCICERO: The surgeons get the last word. Dr. McGrath.

DR. McGRATH: I actually have no global comments at this time, Dr. LoCicero.

DR. LoCICERO: Dr. Olding.

DR. OLDING: I'm not going to beat a dead horse, particularly since I ride one most of the time, but I agree that the sample size seems amazingly small to me given the number of people in the United States that are getting these products injected, and it would go a long way to make me feel more comfortable having a larger sample size, and that's because there are so many variables. Even the term dermal filler really isn't accurate for where we put many of them these days. They're not really just dermal fillers. In fact, we put them into subcutaneous tissue. Around the eyes, we're told to put them as deep as possible. So there's so many variables, it's very difficult to evaluate.

So I would love to see a larger sample size, but it's not an insurmountable problem, but it's certainly a difficult problem that I think has to be addressed based on the durability, the

complications, et cetera. So other than that, I have none.

DR. LoCICERO: Well, the Chair is going to take the prerogative to make one general comment.

One of the things that we've been hearing about today is different areas of the body and how those regions might be similar or dissimilar. And it struck me that the FDA actually has some sort of guidelines on this in that all the time they evaluate and pronounce things substantially equivalent.

So while we go on break, maybe it would be great if somebody from the FDA could sort of give us some insight into how they determine that something is substantially equivalent. Then let's see if we can extrapolate that back toward us. We're talking about different regions of the body that might be substantially equivalent, but save that thought and we'll come back to that after the break.

So we're going to take a break now, and come back at 3:10.

(Off the record.)

(On the record.)

DR. LoCICERO: So you're left with a teaser, sort of a cliffhanger, so to maybe get you back into the room quicker that way.

So the question concerns substantial equivalency of body parts and whether or not the FDA could give us some guidance based on their evaluation of substantial equivalency.

So I believe Dr. Melkerson has a response for us.

MR. MELKERSON: Well, I'll start off with the first issue, substantially equivalent doesn't apply to Class 3.

That being said, one of the questions that we're actually posing in looking to the clinical community as well as industry, as well as the Panel, is are there ways to look, and I think I heard a discussion earlier in the comments, studies are generally aimed or focused at a narrowed indication for use and that's what they get approved for. We face the same issue across device types of they studied X but we know it's going to be used for X, Y and Z. But when you start talking about least burdensome, how do I get to the market? How do I get a broader indication to use once I start with a narrow indication for use or are we thinking about study designs incorrectly and we should be looking at how do you design a broader study to address safety and maybe approaching it from a different concept

saying if the issue is safety, looking at multiple locations for your efficacy, but looking at safety for a broader scope. But those are examples and those are the types of things we'd like the Panel to try to focus in on.

Getting back to the equivalence of locations in the body, I think again I heard in the discussions of the Panel already, some of them are superficial, some are deep dermis, what would make sense to lump together that may be, and again I keep hearing the consensus conference concept but those are the types of discussions that FDA's always open to be entertained, but lacking that, we tend to go with what a company proposes to us and it's usually much easier for them to say, well, they did it. We're going to copy their study that may be a narrow indication but not necessarily where ultimately the products are going to be used.

I don't know if that answers your question or avoided the question, but I hope that gives you feedback.

DR. LoCICERO: At least it brought everybody back.

So are there any other general comments before we proceed?

(No response.)

DR. LoCICERO: Okay. We're going to now focus on the discussion of the FDA questions. Copies of the questions are again provided in the folders for the Panel members. Dr. Dang will present the questions.

DR. DANG: Thank you. So the first question is device effectiveness has been evaluated using validated wrinkle severity and global aesthetic improvement scales. Are these evaluation methods for determining device effectiveness in clinical studies adequate? Are particular evaluation methods more predictive of device effectiveness in the general population than others? And, what is the value of masked versus non-masked evaluation, and live versus photographic evaluation?

DR. LoCICERO: So this is an evaluation of endpoint as the initial discussion. So anybody have comments concerning effectiveness as measured by these methods?

DR. McGRATH: Well, I'll make the first comment on it. With regard to using the validated wrinkle severity and global aesthetic improvement scales, I think those have been adequate for the wrinkle assessment, but I think, and this has been

mentioned already, now that we're talking about augmentation and volume enhancement, I think we're going to have to add something else to that. I don't know exactly if we talk about a global aesthetic improvement scale, I think that would need some refinement to decide exactly what those words mean if we're going to start looking at volume enhancement in deciding whether or not that's accomplishing the aesthetic end. So I think that's something that, number one, needs to be added and, number two, needs to be defined.

DR. LoCICERO: Dr. Burke, you had some ideas before about effectiveness measures. Are these scales really adequate in today's society?

DR. BURKE: Well, I think in a way they're adequate because what we want to have is patient satisfaction with safety, but I think in today's age, we can make quantitative measurements, and we can make quantitative measures about how effective the enhancement is at various time points, and I think that is of interest and I think it is of interest to compare the various in kinds of in plants with each other. So I advocate quantitative measurements.

DR. LoCICERO: Dr. Gooley, how can we use these in a study where we're going to have primary

and secondary endpoints?

DR. GOOLEY: Well, I guess I wonder why a little bit more attention isn't paid to safety as almost a primary endpoint here but --

DR. LoCICERO: Well, that's coming up in another question.

DR. GOOLEY: Okay.

DR. LoCICERO: We're just talking about effectiveness right now.

DR. GOOLEY: Well, I certainly am in no position to say, given my background, what I think an appropriate efficacy measure is but just from a statistical point of view, whatever the community that's expert in the area I think is the appropriate measure to use. You know, it's the statistician's job to make sure that there's a meaningful way to analyze that endpoint and to consider it in the sample size calculations. So I'm not sure I answered your question but I --

DR. LoCICERO: Well, in one case we have something where we eyeball it and say it's one through six, and we have another potential measure that is a continuous variable. So in terms of evaluation, deciding on the number of individuals in the population for effectiveness, give us a little

sense for the sort of studies that would be designed either way.

DR. GOOLEY: In terms of how those things would be evaluated?

DR. LoCICERO: Yeah. We look at it and we say, that looks pretty good. You know, is that going to give us the kind of statistical power that we need or do we need to get more patients in that study or fewer patients and, you know, what about a continuous variable instead.

DR. GOOLEY: Well, in general a continuous variable will require fewer patients than a binary outcome, just a yes, no question but it all depends very much in terms of the sample size. It depends on what your assumed true rates of success or failure for a binary outcome or what your assumed true rates for whatever your continuous outcome are and the difference. That's what dictates the sample size.

So no matter what you use, you just have to make sure that the appropriate statistical methods are employed but as I said, in general, a continuous variable will require a slightly smaller sample size than a yes, no variable.

DR. LoCICERO: Okay. Dr. Newburger.

DR. NEWBURGER: I believe the current

evaluation methods for determining device effectiveness for nasolabial folds are fine for determining nasolabial fold correction, but the way things are going now, we have to go toward new evaluation methods. I believe they should be quantitative, but I want to talk about the population here.

I believe that there are many different populations that are being treated for different purposes, and so even if you take something such as augmentation of the cheek or modification of the shape of the lip, you're going to be looking at people that want correction because of age considerations or trauma or disease or style. For example, what is acceptable as a correction or desirable as a correction in New York is very natural and what you're going to be looking at in the west coast or in the South will be something very different, and it also has great variation depending on which ethnic group is seeking treatment, what the style is. And so I don't think it's fair at that point to use a global assessment scoring system. It's not going to be read the same way.

So understanding that style or definition is something that is still going to be in the eye of

the beholder, there has to be instead an objective way for looking for persistence of the fact, and I think that's what the concentration of quantitation should be focused on, durability.

DR. LoCICERO: Dr. Anderson.

DR. ANDERSON: I would agree with you in principle. Unfortunately, there are very few quantitative scales that are really appropriate for this population. For example, a lot of the self-esteem scales, such as the body esteem scale, refer to areas of the face like satisfaction with the eyes, satisfaction with the nose, satisfaction with the mouth, also the thighs and the waist and the buttocks. So it's very difficult to find a quantitative scales that's been validated that would be appropriate I think for facial corrections other than the nasolabial fold.

DR. NEWBURGER: I beg your pardon, Dr. Anderson. Just because it hasn't been used on a widespread basis doesn't mean that it doesn't exist or that it cannot be devised and validated. That's actually not that much of a challenge.

DR. ANDERSON: right, and that was what I was going to go ahead and add. I was going to say that perhaps development of a scale that addressed

those areas of the body that might be incorporated into the test site, such as the cheek augmentation or something, could be developed. It could be a three or a five question scale that addressed those areas that would be identified, using a Likert scale because it would give you greater variability and give you an opportunity to look for patient satisfaction and differences, but that's an inherent problem. And as I said earlier, I'm really glad that the plastic surgery folks are working on something because we really need it in this area.

DR. LoCICERO: So there's nothing at the moment to grab off the shelf, but in terms of plastic surgery, there is something currently being developed or other literature already available.

DR. OLDING: I actually was going to address the last part of 6(c) which was live versus photographic evaluation. Now, we're moving from nasolabial fold correction to really volumizing of the face, and I'd say the vast majority of the patients that I treat today have more concerns about the volume in their face.

And so there is no fold to correct. There is nothing to measure correctness, but there are now very good photographic methodologies available to

demonstrate the volume pre and post-op and, in fact, one of our members is doing a study of aging on us over the years. And I would think that that would be one way of determining the overall volume because I frankly don't care how it corrects something. I want to know will it fill up that nasolabial fold? Will it fill up the face? And, more importantly, how long will it last?

So I have to be able to tell my patients these days which one lasts the longest in this particular area and if we can have some objective analysis of that volume, I think it'll be important and I think photographically it will go a long way to assist with that.

DR. LoCICERO: Mr. Halpin, so we're talking about development of something new as a tool to evaluate these products. How is industry going to deal with new development of evaluation?

MR. HALPIN: Well, I think when the studies of nasolabial folds were first being constructed, the five point or six point scale had to be developed. So I think it started with target photographs of what was agreed by academia to be a five, a four, a three, a two, a one, and those were developed into one scale where it actually shows the wrinkle as it's

progressing from the worst on the scale to the best on the scale, and I think it's important to note that the best on the scale is not maximum correction but the optimum correction, and one of the things we found in developing these scales is that the photographs are very good for educating someone on how to use the scale, but it's a question as to whether you can take that scale and compare it to a photograph or whether you have to compare it to a live face.

So I think part of that has to be left up to what you're actually trying to do and what the industry or the sponsor actually feels is the most appropriate way, but I think it would be very much within industry's capability to work with academia to create those types of scales for different areas, keeping in mind that it's not entirely quantitative as much as it is you're trying to get an optimized effect. And, ultimately the goal is, is the patient very satisfied? Did they get the correction they wanted? And when you observe it visually with your eyes, is that what you're actually trying to achieve rather than did it go three millimeters or achieve some quantitative scale.

DR. LoCICERO: So Polaroid is going out of

business or has been out of business. You're about to run out of film sometime in 2009. So we're going to be going to digital photos, and I can on my iPhone morph a face to look like anything I want. So how are we going to deal with this issue in terms of evaluation? Dr. Walker.

DR. WALKER: Dr. McGrath can speak to that.

DR. McGRATH: We already have those systems in place. For example, for our trainees who are taking board exams, there are devices that you use that show that a photograph has not been altered. It has to be present on the corner of the photograph if they're to sit for board certification to show those cases. So those things are already in place if that's what you're alluding to, to ensure honesty and accurate photography. That methodology is already out there.

DR. LoCICERO: Okay. If we're considering using photographs, is it still necessary to mask our evaluators? We're all becoming quite sophisticated figuring out what stuff is. Physicians are very good at sleuthing out subtle differences. So is it still necessary to try to mask them? First, Dr. Burke.

DR. BURKE: I think it definitely helps decrease bias, and we don't mean to have bias but

those of us that have even counted cells in microscopes know that if you want a result, you kind of, if the thing is on the border, you count differently perhaps. So I think it's so much better to do everything, to do things masked because it alleviates one subjective variable. It removes one subjective variable.

DR. LoCICERO: Dr. McGrath.

DR. McGRATH: Yeah, and I was going to say I think that particularly when we get into the issue of volume enhancement, blinding will be very useful because I think many of these will be much more subtle changes and I think it will be interesting to see whether, and this will be a learning experience. This is all very exciting because this is new. If people put a certain amount of a product into perhaps build up the malar area or the chin, I mean how much do you need to see a difference, and I think that it would be very useful to have people be blinded to the befores and the afters and so forth because it'll start to give us a lot of information about how much change you want to achieve, you can achieve, how much is suitable, and that type of information.

DR. LoCICERO: Dr. Li.

DR. LI: I don't know how practical or

impractical this is, but in other areas where we've had to deal with subjective rating systems, we've actually found that multiple observers often give you a little more information than blinded. So you can basically get some of then the skew or the different ways of the different subjective ratings.

So numerically, if it's possible to have multiple observers, especially in some cases as someone pointed out, you really can't do a blinded or a masked protocol. In that case, I think multiple observers might be an alternative.

DR. LoCICERO: Dr. Gooley, is there a way to adjust an evaluator based on their bias?

DR. GOOLEY: Well, if you have multiple observers, you have to alter your statistical techniques to evaluate things, but that's certainly doable.

DR. LoCICERO: If you had one person who was really hard, another person who was really easy, could you level a playing field?

DR. GOOLEY: Are they judging the same -- the hard person and the easy person are judging the same patient?

DR. LoCICERO: Yes.

DR. GOOLEY: Well, if the hard person and

the easy person, as long as they do all the patients, you can control for that, yeah. It's a little bit more complicated to do an analysis like that, but it certainly is doable.

DR. LoCICERO: Dr. Newburger.

DR. NEWBURGER: If you have some patient subjects being untreated for a period of time, but the observers don't know who's being untreated and, for example, start someone at month two or month three of the protocol as their treatment date, but don't let the observers who's actually being treated, you should have a way to suss out who's hard and who's easy and that should perhaps uncover some bias.

DR. OLDING: I might add one thing. If you do have multiple observers, that does increase your variability a bit. It might increase your sample size requirements somewhat if that's taken into account in the sample size estimates.

DR. LoCICERO: Okay. Mr. Melkerson, on this question, has the Panel provided sufficient information for the FDA?

MR. MELKERSON: Yes. Thank you very much.

DR. DANG: So the next question covers some safety questions. Are the evaluation methods used to determine device safety adequate? Should current

safety evaluations be expanded to include larger studies to detect adverse events that may occur at a lower frequency, studies of longer duration to detect delayed onset of adverse events, and/or histological evaluation of biopsy samples?

DR. LoCICERO: Thank you. Okay. Dr. Gooley, here's your safety question.

DR. GOOLEY: Yes is my answer.

DR. LoCICERO: Spoken like a true statistician that's for sure. Dr. Bigby.

DR. BIGBY: So I think in order for the FDA to ask a Panel this question, they need to be clear about how they define a serious adverse event. You know, there are some standard definitions such as it requires hospitalization or intervention of a doctor. And, what frequency of serious adverse events they would consider unacceptable. I mean as a Panel member, I have no idea what that is in their minds.

The same thing is true for non-serious adverse events, you know, define the adverse events that they're interested in and at what frequency they would become unacceptable.

And then I think as you go about answering this question, clearly if you are talking about events that occur, anything less than, you know, five

percent of the time, none of the studies have been adequate but we don't really know what is your threshold for considering something either too frequent or too serious.

DR. LoCICERO: Dr. Walker.

DR. WALKER: My immediate answer would be, yes, all the above as well. However, I'm particularly concerned about the studies for longer duration. With the newer products that are coming in the market, I think there should be some way for the study design to reflect the duration that is intended and then have some parameter to look at what a longer duration would actually mean. Does that mean if a product lasts for 6 months, should it be studied for 12 or possibly 18? If a product is supposedly lasting for two to five years, what would actually be considered a delay onset and how long should it be looked at?

So I'm thinking some parameter of either double or triple the amount of time. I mean that may not be feasible but that's what a delayed onset issue would really require, and there's no way to really quantitate that. Some of the earlier studies, we're looking at products that were basically looking at a three to six month duration. So 12 months was

probably adequate. If, in fact, the duration is 12 to 18 months, what's an adequate longer duration to really detect the delayed onset of these adverse events which is a major concern I think.

DR. LoCICERO: Dr. Li, do you have any thoughts about that?

DR. LI: I have a couple. One, I guess what I'm hesitating for is most of these materials actually have a long history in medical implants, methyl methacrylate, hydroxylapatite, polylactic acid, actually have long histories as implant materials in other devices. And there's some lessons to be learned from there, although they're not exactly on point because of, you know, the dose response issue and other material factors.

So I'm not quite sure how to -- I'm just sitting here trying to figure how to meld all that into something intelligent, but I haven't got there yet. One issue for instance is the histological evaluation of the biology samples. Although as a scientist I'm always interested in looking at histology, but I don't really know why we're looking at it if we can't associate the histology with some significant clinical event. My experience is if you implant particles in tissue, any tissue, and come

back and look in a few weeks, you're going to see some cellular response you'd rather not see. But whether or not that actually goes onto have a clinical consequence is a completely different question.

So I guess it seems to be more of a very research project, for instance, on the histology unless there's a specific clinical endpoint that we're trying to reach, and I guess in the discussion yet, the clinicians will have to tell me if there's some clinical endpoint that we could relate to histology. In the absence of that, I'm not sure requiring histology gets us anywhere.

And I guess I would say the same thing for the other things, to look at, unless there's some significant clinical event that we're trying to explain, I think just looking may not advance our knowledge.

Actually one follow-up. I'll just get on my soapbox for one thing. And I guess the reason for the confusion is the thing that's kind of lacking in here is what I'll call basic understanding of the effect of these materials, their particle size and their dose as a function of some clinical event. In other areas, for instance, we know -- I've spent my

life actually interesting enough trying to avoid the generation of small particles in implants and here's this whole area of where they purposely put in small particles. So it takes me back a little bit because you're doing things that I've spent a lifetime trying to avoid.

That being said, it seems like it's, you know, on the scheme of things not all that bad, right, because most of the patients seem to be doing okay, but on the other hand, there seems to be a small group that doesn't do that great. And so I'm not quite sure why in the absence of some basic information.

So maybe one thing I could offer the companies is, if you really want to get to the bottom of this, fund some basic research or if you're a clinician, you know, apply for a NIH grant and get some basic studies done because I think in the absence of that, we're always going to be bumping around in here trying to figure out what the heck we're doing.

DR. LoCICERO: Mr. Halpin.

MR. HALPIN: With regard to safety, I think a lot of it is very specific to the material as Dr. Li just pointed out, and I think most

manufacturers have a lot of preclinical material on their products. I know that many manufacturers actually control their particle sizes based on what they perceive will be issues if they don't control them.

I think from a safety point of view, if you look at the clinical trials we currently do, procedural related adverse events may be as much as 80 percent of patients. They may have multiple procedural related adverse events and then underneath that are some adverse events during clinical trials which appear to be device related for whatever reason and may occur somewhat later during the duration of the product.

Most manufacturers I believe have a good idea of what the residence time or the durational effect of their product is, particularly when they're doing a pivotal clinical trial. So I think they have a good feel for how long to study the product.

I believe that most of these clinical trials are done with very standardized injection techniques. If you look at what we saw earlier today with MDRs, I think maybe in 2007, there were 2 million dermal filler injections, and there were maybe 130 MDRs reported, obviously underreporting,

but you're detecting something in the 5 in 100,000 range if you try and go out and actually study that. And I think that given the idea of trying to establish the base safety and effectiveness of a product in a given indication, to have these large safety studies may be more than is required and not only that, I'm not sure you would achieve your endpoint in doing that.

I think in certain focused situations where you have a permanent product or something, it may be unique to that product that you need to have a slightly different study design.

And I think histological evaluation, we actually do a lot of preclinical testing and follow ISO 10993 guidelines prior and during clinical trials and some of that information would be available in order to determine what is happening with that product in the tissue situation and how it's actually resorbing.

DR. LoCICERO: Ms. Rue, from a consumer's standpoint, longer trials, bigger trials.

MS. RUE: From everything I've heard, I don't know that the trials would vary as opposed to getting consumers to give feedback because, you know, we can study things forever but somebody's always

going to fall out of the time period of the study frame, and again I think it's up to a lot of consumer education and follow-up with them and giving them the tools they need to get the feedback and the results they have, both positive and negative.

DR. LoCICERO: Dr. Anderson.

DR. ANDERSON: I agree with you about feedback. I think that a very long study would create real problems in being lost to follow-up.

But I wanted to address the histological question. I think that asking a patient who's happy with a cosmetic result to submit to a facial biopsy is going to be problematic to say the least. The only way I can think to get around that, if it is something that the Panel or the FDA would feel is necessary, is that I suppose if they have test dose on another site in the body, a biopsy could be taken from the test site, but I really think histological evaluation of biopsy in a cosmetically improved area is something patients are just not going to do.

DR. LoCICERO: Dr. Newburger.

DR. NEWBURGER: I think histology is of tremendous import and certainly it would not be taken from a cosmetically important area but there's nothing wrong with placing the implant in volar

forearm or another cosmetically insignificant area and seeing what happens over the course of time, and I think it would be helpful going forward to see if there's a substantial foreign body reaction that's seen microscopically if there's a device where the effect persists for a very long period of time and it is theorized to cause new collagen to form, I'd want to know, is that collagen normal collagen or is, in fact, controlled scar formation? Clinically, I certainly see people who have been injected with certain devices for volumizing, if they come to me and I'm trying to inject through the same site, there's a resistance as though I am, in fact, injecting through scar tissue. So there is actually a change in the skin that's not normal. I think this is helpful particularly going down the road.

And another issue in terms of studying more comprehensively the basic science of the devices, before it goes into the clinic, is if you don't know really how the device is metabolized or handled, you're really at a disadvantage. There was, I can't remember which particular sponsor it was, but there was a device that was before Panel and the comment was made and it does not migrate. And my question was, how do you know? Because we don't see it. But

have you looked for it? Have you biopsied in animals, reaching the lymph nodes. Have you looked for it systematically? Well, no, we haven't. Then how can you make that statement? We need a lot more basic information I believe. So if we have that information, then the longer term studies might not be as necessary, and certainly fewer postmarket studies.

DR. LoCICERO: So I'll try to summarize this at this point. We seem to be in favor of larger studies. Longer studies are probably not going to be feasible because of loss to follow-up problems and that we have looked at the pros and cons of histology and there are significant pros and cons on either side. Is that a fair summary?

DR. OLDING: I would just like to add one thing about the histological. I forget the percentage of adverse reports on patients that had to go to the operating room to have the material removed, but that would seem like the key code of unlocking what the problem is, and I would hope that we make every effort to get those specimens from the companies.

DR. LoCICERO: Okay. Mr. Melkerson -- we've got one more.

DR. McGRATH: Just before we close this, your summation, I think I agree with but I think that we agreed that perhaps larger studies to detect adverse events are universally considered useful but we're not going to be able to expand them to the size where they're gross epidemiologic studies. That's not what we're talking about. There I think we're still going to be relying on adverse event reporting. So we don't want to have embarrassingly small studies of 100 patients, but I don't think we're going to be able to do great global, you know, population studies to get at these rare events. That's going to have to come through something else besides the studies.

And in terms of the longer duration, you said, no, because we're recognizing the problems but I don't think we saying that. I think we're saying for the non-absorbables, we're possibly saying yes, at least some of us are, that we'd like to see them longer but not necessarily for some of the absorbable ones that are gone quickly.

DR. LoCICERO: So there's going to be a difference in effectiveness and safety in terms of the number we look at. Effectiveness is biostatistical and safety is really by incident, and that in some cases, the studies may need to be longer

because of the implant duration. Is that now a fair summary?

(No response.)

DR. LoCICERO: Mr. Melkerson, does that satisfy -- one more.

DR. LI: Just as an add on, on that, we have to be a little bit careful about that because polylactic acid is clearly, I think we'd all put that on the resorbable category but we know in other applications there is late immune responses three to five years after implantation for polylactic acid. So this is something that is, in fact, supposed to resorb and to get back to Dr. Newburger's issue, I don't really feel we know exactly what happens to any of these materials over time. We've seen the volume that may disappear, for instance, if it's a volume filler, but we don't know how much is left or where it went. Polyethylene particles generated in a joint replacement are found all over the body, in the lymph nodes, in the lungs. There's no stopping the particles when they get down to be less than a micron in size. And we have no idea where these particles are ending up that we're putting in, but you might say that we're putting in 25 to 50 micron particles but if they resorb down to nothing, somewhere along

that size range, they're in a size that's very biologically active and mobile, and we just really don't know where they're going.

Now, as it turns out, maybe they aren't doing any harm but that doesn't mean that we actually don't know where they're going or what they're doing.

DR. LoCICERO: And I guess the other thing is that for effectiveness, we're pretty clear but it rests with industry to make that proof, but that in the safety area that we need to put some of the obligation on the consumer to be responsible and report. Does this answer your question?

MR. MELKERSON: It's sufficient. Thank you.

DR. DANG: Thank you. So the next couple of questions continue to this query about clinical study design. Do the inclusion/exclusion criteria utilized in these studies allow for collection of safety and effectiveness data that are consistent with and predictive of your experience with dermal fillers in the post-market setting, such as personal practice, published literature and the FDA presented data from earlier this morning?

Does the exclusion from clinical study participation of subjects who have had recent

cosmetic procedures, such as other dermal fillers, laser and chemical treatments, botulinum toxin type A, and so forth, impact the manufacturer's ability to collect complete safety information?

DR. LoCICERO: We need some information from those who have done investigations on these products. Does anybody want to -- Dr. Burke.

DR. BURKE: Well, I think the criteria as stated in the studies were fine and I think that I agree with that with my clinical practice, and I think for the next question, there's no way you would study one filler on top of another. I mean you certainly can find patients that have not had fillers but already we're talking about all of these gray zones, and to put one filler with another, although that will happen in the general population, you can't do that as the start for your study.

DR. LoCICERO: Other comments?

DR. McGRATH: I have a question of that second question. I guess I would ask that's certainly true if you're using other fillers in the same area but, for example, if you're using Botox for another application, how would that have any impact if it were not Botox in the same area that you're evaluating?

DR. BURKE: Well, I guess you could say you could have had a filler that we know from clinical experience, like Zyderm type of filler, if you had that 10 years ago or even 4 years ago, it would be okay, but you certainly would not want any of the longer term fillers that we are talking about as part of the fillers in the population of fillers today. I mean you wouldn't want to have a more permanent filler within say four or five years, and you can find patients that haven't had that.

DR. OLDING: If I could just make another comment. It may also affect the evaluation of the overall global aesthetic value at the end. That could be very confusing I think ultimately.

DR. LoCICERO: So you would have to limit it to less than 40 procedures before -- yes.

DR. ANDERSON: Yes, that was my point as well. If you're looking at the face and you're saying how satisfied you are with it, if you just had a filler and perhaps some Botox, your overall satisfaction may be higher as a result of the Botox, too.

But another question and the scientists here would need to answer is, is if we don't allow them to use multiple agents, are we going to know if

there's an interaction?

DR. LoCICERO: Anybody want to tackle that one? Dr. Newburger.

DR. NEWBURGER: One of the individuals who wrote a letter to the Panel suggested that patients who have fillers be given a registration such as we would have with Accutane and the eye pledge program and that way if adverse events were reported later, you could see how many of these were from multiple fillers. In my own practice, the few patients who have had persistent swelling and inflammation, just about every single one of them has been, and I'm taking a further history, and they all have complete histories in terms of previous procedures, will seem to recollect, oh, you know, I had silicone injections 20 years ago or 25 years ago around there, and so of all the previously injected devices, that does seem to have a common denominator in the ones I see.

By the way, in terms of the inclusion and the exclusion criteria, in the studies, when I get the consent from the rheumatologist I routinely use this in people with connective tissue diseases, who don't have active disease, we've never had any problems and that's several hundred at this point, and also do inject it on patients with anticoagulant

therapy, with their desire to have it done understanding that they will bruise more extensively, and we've had no issues whatsoever.

DR. LoCICERO: Other comments? Mr. Melkerson.

MR. MELKERSON: Just a slight variation to this question. We've talked about other fillers, but one of the things I thought I've heard in previous discussions was repeated application of the same product for the same area and how does that impact your discussion at this point?

DR. LoCICERO: Dr. Newburger.

DR. NEWBURGER: One of the issues that we've encountered, and we do use fillers off-label, is when people have come in who have had, for example, in the lip area, where there is a very, very thin dermis, that had multiple injections along the lip margins and in the pulp of the lip, it's very difficult. You will tend to have more lumps develop if you're not careful because of the scarring which develops in that area after multiple procedures. Certainly you have a larger area with which to introduce your needle when you're dealing with a larger anatomic area but scarring can change the picture over time.

DR. McGRATH: I think your only real answer to that question is you're going to have to sort out the patients that have had repeat treatments and who haven't because I thought about that when we were talking about the question of longer duration of studies. I mean a lot of patients will go back and have the product supplemented at intervals. And so if you follow them for five years, you're not going to have many people say, I'll never have it again so I can go through the five years.

So I think it's just going to have to be sorted into two groups, one for the persons who have had it, you know, only once, and another for people who have had repeated, multiple times and I think those are two different endpoints. I don't see how frankly that would be avoidable.

DR. LoCICERO: I think we've kind of discussed the pros and cons of both the inclusion and exclusion criteria. Is this sufficient for the FDA?

MR. MELKERSON: Yes. Thank you.

DR. LoCICERO: Okay.

DR. DANG: Moving along, are current methods for determining sensitization potential adequate, such as preclinical study methods, an animal study or clinical study methods, such as by

evaluating adverse events after multiple injections? And as individuals have the potential to receive numerous injections of dermal fillers within a lifetime, should the study methods for determining sensitization potential be designed to be more reflective of the frequency of dermal filler injection in actual clinical use?

DR. LoCICERO: Comments?

DR. OLDING: Could we have somebody explain to us what the Magnusson-Kligman maximization test is, since I tried to look it up and couldn't find it?

DR. DANG: I think that's also known as the Guinea Pig Sensitization Test. Is that clear enough or --

DR. BIGBY: As what?

DR. DANG: Guinea Pig Sensitization Test, where the guinea pig would be injected with a liquid extract or a liquid form of the material and then they'll be introduced to the device or subject material again in a patch, an inclusive patch or another injection a couple of months later to see if there's an immune response.

DR. LoCICERO: Dr. Newburger has a lot of experience with repeat injection. Maybe she has something to say.

DR. NEWBURGER: I think that the current methods are adequate. With the early exception of the product that had a bovine origin, to have a true allergic reaction is, you know, certainly very rare. We've not seen one in our practice and in the community, I've not heard of any true allergic reactions. I think the current methods are fine anecdotally.

DR. LoCICERO: Dr. Li.

DR. LI: I'm not sure how we answer this question because I always seem to be kind going around in a circle because if we don't know the histology of what's happening in the patient, and we do some animal tests, a guinea pig or, you know, patch model on the back of a rat or something like that, we're going to get some tissue response from that animal but unless we know what the tissue response is on the person, I'm not actually sure how one set of data affects the other.

So I think again if you can tell me that the histology in the guinea pig looks like the histology somewhere at the implantation site, then I say great. Let's do that but if the histology is completely different, I have no idea what that means.

DR. LoCICERO: Do we have some idea of

those who wind up getting dermal filler, what the average number of times they get the filler over several years?

DR. OLDING: For me, it depends entirely on the filler and on the age of the patient but for many of the hyaluronic acid patients, my patients come in every six months. So rather than go from empty to full, they go partially empty and then back and forth. So they oscillate at a more even pattern. But I mean I've had patients since we first approved Restylane that have, for example, just one of the earliest, I think the earliest hyaluronic that was approved, that have been getting that the entire time.

DR. LoCICERO: So we probably would say that it's already happening in the real world?

DR. OLDING: Certainly. Absolutely.

DR. LoCICERO: I'm not sure we can give you much further guidance, Mr. Melkerson. Is this satisfactory for this question?

DR. MELKERSON: Yes, I'll just make one comment that a lot of the work with the products is going to be material source dependent because allergic reaction are not just bovine. It could be avian for some of the hyaluronic acid based products,

but a lot of them have gone to bacterial sourcing. So those questions have been going away with time.

DR. DANG: This is a question regarding post-approval studies. If a post-approval study is recommended for current indications for use, please suggest the appropriate study design, comparison group, length of follow-up, validated assessment method and safety and/or effectiveness endpoints.

And I believe your responses were yes earlier.

DR. LoCICERO: No, it was no.

DR. DANG: It was no. Okay. Then never mind the second part of this question.

DR. LoCICERO: Okay. So we're just going to answer the first part of that. We've been talking about how we need to establish something that's the same for everybody, at least has the same criteria. Here's our opportunity to say what those criteria should be at last in broad terms. So maybe Dr. Li can start.

DR. LI: Thank you. Well, I'm caught right off the bat. I'm not exactly sure how to do this because it seems as if it's not clinically sensible to set an amount injected and make that across the board for every patient because that kind of takes

the effectiveness future out of it. But conversely, if you go to the same amount of effectiveness, then you've got some other variables going on. So I'm a little bit trapped. Maybe Dr. Gooley could help me out of that, help me out of that trap.

But that aside, it seems like, you know, it seems like the effectiveness variables are well discussed and well at hand although there's some discussion over some details but on the safety side, I agree with Dr. Gooley, that there seems to be some other factors that could be included for evaluation.

DR. LoCICERO: Let me just get some clarification from FDA here. If I recall correctly, most of these products were approved with conditions requiring a postmarket study or about the safety or about those patients IV, V and VI who were not included.

DR. MELKERSON: I'll try and dance around this a little bit, but for each particular product, there are, from what I'm hearing around the table, there are short-term and long-term questions, when you're saying a product is relatively safe and effect to go to market, are there any long-term issues, and I think I've heard, training as being an issue? Post-approval studies can address whatever questions

do come up with that particular product. So issues of general population, in other words, it was studied at Premier Centers. Well, now it's being used in the general surgical community. Is that representative? Those are types of questions that would be the basis of post-approval studies, and I'm going to actually look over my shoulder and defer to our OSB folks to give other ideas or comments that they would make on post-approval studies.

MS. SHOAIBI: I actually lost you in the middle of the question. If you could repeat the question, I would appreciate that.

DR. LoCICERO: The question was specifically the products that have been approved and required postmarket studies, were either about the inclusion criteria or about questions of safety.

MS. SHOAIBI: The objective of all of the post-approval studies that have been completed, three post-approval studies have been completed for eight products, and the objective of all of those was safety, safety issues and as I mentioned, even optimal aesthetic results data were not collected for two of those studies. So the objective was only safety and with emphasis on the primary adverse events that was listed.

DR. LoCICERO: Great. Thank you. So --

DR. LI: First let me apologize. I answered the wrong question. I'm sorry. I had a question though, before you asked your question, a question for Dr. Olding. If your patients are getting essentially another injection every six months, for instance for the Restylane, then how would you interpret the results of following any patient for several years because every six months they're getting another injection? So I'm not quite sure what a long-term follow-up tells us if they're getting a new injection every six months.

DR. OLDING: I'm not certain exactly what you're getting at. Are you asking me how do we evaluate the effectiveness of a product which is reinjected on a periodic basis every six months for a long time? Or are you asking --

DR. LI: Yes, that would be one part of the question. The other question is, in some sense, is it really a long-term study if you're giving a new injection every six months?

DR. OLDING: Well, it's not meant to be a long-term study. It doesn't --

DR. LI: I'm not questioning your practice. I'm asking in the spirit of designing a clinical

study but if in real life, you're going to give a patient an injection every six months, maybe somebody else can help me out making my question clearer.

DR. OLDING: Well, there are two scenarios. One where you're injected once. You can evaluate that patient long term. The second one, and I think Dr. Newburger alluded to that, there can be changes that can occur from the periodic injections that are in and of themselves different than what would happen with one injection. So it may not be a long-term study in giving it for three years and then stopping and looking at something, but it certainly reflects the clinical practice and therefore looking at those patients long term, I think is appropriate.

DR. LoCICERO: Dr. Burke.

DR. BURKE: Well, I think the whole point of a long-term study, first of all, that would only be indicated for things that we know are not absorbable in a relatively short time, meaning months or maybe a year. So things that are going to not be reabsorbed should be looked at I think longer term, and the whole point of the long term study is that we don't see some small, some effects that are not very frequent but may, in fact, be serious that might come later. So it is worth following some population of

people that have had something injected that is non-absorbable for some time. And even if you're putting it in again, you want more people to look for these infrequent adverse effects and you want longer times just for the non-absorbable implants.

DR. LoCICERO: I'm going to relate kind of an interesting story and ask a question of Ms. Rue. We have had patients who've had a valve implant and three years later they have no clue what they had done. They don't even know they got a valve in place. So is there any way that we can expect our consumers to know what they had injected three years ago after they had multiple injections?

MS. RUE: Well, I think the group that this population is dealing with is a little bit more involved in what they're doing because it's elective and it's something they're doing to improve their appearance and it's a self-esteem issue, but also it's not so much what they had done. It's where they had it done and the fact that they had it done and what their outcomes were.

DR. LoCICERO: Dr. Newburger.

DR. NEWBURGER: Our patients don't have to deal with the amnesia post-general anesthesia and perhaps they'll have clearer recall.

DR. LoCICERO: We're doing them under local now. Kidding. Not quite.

DR. NEWBURGER: Next year.

DR. LoCICERO: Not quite. But, no, do your patients, can they tell you I had this product six months ago and that product two years ago?

DR. NEWBURGER: Except for the ones that forgot they had silicone 20 years ago until they got a reaction, generally they're fairly accurate. I like the way this filler holds up better than the last one. So let's go with this one. They remember.

DR. LoCICERO: Dr. Walker.

DR. WALKER: Yeah, I would agree that the patients for the most part seem to be quite familiar with the product that they use and can report that, but as the number of products increases, I think that's going to be a harder question to answer down the road because the names are very similar, they know they had a hyaluronic acid filler. They may not be 100 percent sure which one. I think there could be some confusion in the future because of the number of products. I think even five years ago, this was probably a question we would have to even remotely address. But now going into the future, that's probably a different story.

DR. BURKE: But I think first of all, this population of patients are intelligent and very concerned as you just said and we all have to keep our medical records five or seven years. I mean I always like to know what a patient had before, and before I inject them with something, just for completeness, I have them call the doctor to see what did they have, but again, there haven't been that many things available in America until now. So we were pretty sure we knew what the person had but I think that at least for the past five years, they could always get their records. They could always just make a phone call and find what they had the last time or in that period of time.

DR. LoCICERO: We're sort at a watershed here. The FDA and the Panel both have sort of beaten up these postmarket studies a lot, and now we have no recommendations. We need to come up with something that will help out here. Yes, Ms. Rue.

MS. RUE: Well, I think we heard Dr. Gold and several others talk about the consortium and getting the group together, and I think, and since I'm not voting, I can't personally recommend it but I think it's something that the Panel needs to consider and have the groups that are very actively involved

in this from different sides and come up with the recommendations for this because they have a lot of the information and are working with a lot of the population groups, and that would be a great place to start.

DR. LoCICERO: We're depending a lot on a consensus panel to help us out here, and the development of a guidance document, and we don't have a sponsor in front of us that is going to tell us, oh, yeah, we're certainly going to do that and then, you know, they'll promise anything to get approval.

I'm concerned about the fact that we're going to come up with something that won't happen. We'll make a recommendation that's not going to happen. So I just want -- our groups are gone unfortunately but I think after this, we're going to need to be sure that those societies who propose this are willing to go along with a consensus group.

So, Mr. Halpin.

MR. HALPIN: I just wanted to comment that it seems to me that we're being asked if there is a one size fits all post-approval study design. I'm not sure that I can find one that I would recommend. I think some of these products are very different from each other and have very different unanswered

questions when they get to the point of approval. And so I think it may be beyond the ability of sitting down in one meeting to actually come up with a one size fits all design, and it may be better on a case-by-case basis as you're seeing new products to try and establish what would be a question you can't answer in a pre-approval study very easily but is an important question to answer. That may be part of what we're struggling with.

DR. LoCICERO: Dr. Gooley.

DR. GOOLEY: Yeah, I completely agree with that and I think every effort should be made, and in some cases it's probably not doable, but I agree with Dr. Zuckerman who spoke earlier. I think every effort should be made to address all these questions in the premarket study. Now, you don't know what issues might come up but I think the premarket, this doesn't directly address the question, but I think the premarket study should be designed to try and minimize the questions that might come up in post-approval studies.

DR. LoCICERO: Mr. Melkerson.

MR. MELKERSON: A representative from our EPI group would like to ask a question of the Panel and maybe help the discussion.

MS. MARINAC-DABIC: My name is Danica Marinac-Dabic. I am the Chief of Epidemiology which is the unit that is in charge of post-approval studies. I just would like to ask a couple of questions for clarification. As the FDA would have legal authority to request the post approval studies to address safety, continuing safety and effectiveness and reliability of the approved products.

Now, I understand that you do not recommend the post-approval studies generally speaking as I understand from your discussion if the specific group representation of subgroups is in premarket studies.

I would like to get the Panel opinion about, and with your understanding, every PMA that comes to the FDA is going to be evaluated based on the data that come from that PMA, meaning that if the data are problematic or if there are some issues with the representations, we will identify the specific questions that ought to be addressed postmarket.

So in that spirit, I would like to ask you, and the reason for my question is because of the history and the Panel recommendations in the past, that those post-approval studies should be looking only into safety issues. If, for example, there are

specific issues for which we believe postmarket studies are needed, would you still recommend that both effectiveness and safety would be done in those studies in case the premarket data have some limitations? That's the key issue for our epidemiology program in order to make sure that we are not bound only on the safety or effectiveness or both.

DR. LoCICERO: I'm going to take the prerogative of the Chair here. The Panels that I've been associated with, and I think the spirit of the Panel is to review your analysis, review the data, deliberate and make a recommendation based upon our interpretation and what we feel is appropriate and that if that includes effectiveness, that will be made. If it includes safety, those will be made.

MS. MARINAC-DABIC: Thank you very much.

DR. LoCICERO: Okay. So if I were a chair of a hospital committee, I would now table this and form a subcommittee and I'm afraid that's where we stand at this point. The -- question, really this is something that a consensus really needs to help with but before we make a final recommendation, who should sit at that table? Who should be part of this consensus conference? Speak up.

MS. RUE: Industry and consumer.

DR. LoCICERO: Industry, consumer.

MS. RUE: Industry and consumer for sure.

DR. LoCICERO: Thank you, Mr. Rue.

MR. HALPIN: Academia and the FDA.

DR. LoCICERO: Okay. Any others? So academia meaning universities?

MR. HALPIN: Universities or societies, academic societies that have an interest in this area. So a lot of the folks who were talking today.

DR. LoCICERO: Okay. Well, that's different because that maybe collection of practitioners who may or may not be very academic but may also have the patient as their most important interest, but they may not be very academic but they may be the biggest users. Am I stating that correctly, everybody?

MR. HALPIN: And some other examples I've seen, there have been requests from the FDA, not saying that has to be the case in this situation, where they're actually asking for input on existing guidance documents that may be out of date, and organizations have gotten together to actually go through a process to meet, have sub-working groups and actually update or develop those guidance

documents. So that may be an option.

DR. LoCICERO: I think what we're saying, Mr. Melkerson, is that this consensus panel which would give you some further guidance in this area is going to need to take not only the traditional FDA components of sponsor, academic, investigator and FDA but also the end user who is the person who is on the syringe side of the needle, as I think we've heard earlier, and the person at the other end of the needle, the consumer. So those groups would need to be represented to give you the kind of information you really need.

Is this sufficient for this question?

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

DR. DANG: Another couple of related questions. Injection into nasolabial folds has been considered representative of dermal filler use to correct moderate to severe wrinkles. Can the use of dermal fillers for augmentation of tissue volume and for recontouring of tissues, such as non-surgical rhinoplasty, lip augmentation, under eye injection and hand volume restoration, be considered an extension of filler use for wrinkle correction? What areas of the face would be considered as having

tissue structure and physiology that are dissimilar to nasolabial folds?

And a further follow-up, can the safety and effectiveness data collected from randomized, controlled clinical trials that studied the injection of dermal fillers into nasolabial folds be considered predictive of their safety and effectiveness for any of the new indications that have been discussed today? Or, are such uses dissimilar to use in nasolabial folds such that they would warrant new clinical studies?

DR. LoCICERO: Okay. So this is the question back at us I think in terms of substantial equivalency of body parts. Dr. Li, I know that you have a lot of experience with hips, but there are other joints that were involved at a later time. Were those areas considered equivalent or were there specific new areas that were looked at? Can you give us some guidance in developing something here?

DR. LI: Well, depending on the device and the material, it could be location sensitive. So I don't think there's a universal answer to that question which means I think that you, not knowing anything else, I think you have to consider using a device or a material in a different site a

potentially dissimilar reaction to that device. In fact, we have some examples of these in these off-label uses where for instance the use of some of these devices in the periorbital area doesn't really seem to work that well. And it's not quite clear if it's a tissue response or something else.

So I feel that we know so little actually about the mechanism of action of these devices that I think it would be a mistake to consider use in a different area other than nasolabial fold as being a similar case. So I think in every case, I would want some study to be done.

Did I answer your question?

DR. LoCICERO: Yes. Dr. Newburger.

DR. NEWBURGER: I agree with Dr. Li completely. I don't think it's analogous placing a filler in the dermis to placing it just at the periosteum or on top of cartilage and I think there do have to be separate studies for these areas, and there's maybe one or two folds that I might consider similar but in general, the vast majority of these are not the same and certainly hand volume restoration is an entirely different circumstance and that needs its own study.

DR. LI: I agree.

DR. LoCICERO: Dr. McGrath, any comment?

DR. McGRATH: No. For that question, I agree.

DR. LoCICERO: Dr. Bigby.

DR. BIGBY: I agree with what was said in that the answer to the question is no. However, there is a large body of use of these products in those other areas and not much of a signal has been detected in terms of adverse events occurring.

DR. LoCICERO: Do you think that's due to the fact that there are very few adverse events or that people are unwilling to report a non-indicated use adverse event?

DR. BIGBY: I think the former because, you know, just think about this. From the physician's perspective, I actually was involved in a study of adverse skin reactions to drugs and, you know, if a drug causes a reaction and as a physician you get called with a rash for every 20 patients, you're going to stop giving that drug. And the same thing I think is true for injections. If physicians are having a lot of adverse reactions, you know, and people calling them and being unhappy with results and suing them, I think they wouldn't be doing so many of these procedures.

DR. LoCICERO: Other comments? I think what we're saying is that there really is no way to translate the data to another area, that we can't determine at least in a short-time period that there's any substantially equivalent area in the body.

MR. MELKERSON: May I push my question back on you a little bit further? We heard that some of these things are dissimilar. Kind of the corollary to that, are there things that are similar like when you're saying cheek augmentation or other chin augmentation? Are there things that could potentially be grouped together based on where they're being implanted or the type of material being used? Kind of think of it from that perspective.

DR. LoCICERO: Yeah, Dr. McGrath.

DR. McGRATH: I don't know if you can group them by anatomy as much as you can group them by what you're looking at. You know, if you really look at the product, I think that a lot of the questions about the product per se are going to be the same no matter where it's used. So what you have to sort out is what those things are that you don't need to look at in new studies, allergic reactions.

But on the other hand, the things that

aren't going to be translatable from one place to another will be the effect on other anatomic structures, the technique that the person uses there. So I think that when you craft the pieces that look at it, that's what you're going to be focusing on.

So I wouldn't separate it by saying this geography is the same. I'd separate it by what do you need to look at and what don't you need to look at because you don't need to look at everything from scratch just because it translates to a new spot.

DR. LoCICERO: So, Mr. Halpin, if the FDA were to say that it were a little easier to get another indication, that you weren't going to have to look specifically at allergic reactions, et cetera, that you could change your form, would that be something that industry would be more apt to go for additional indications?

MR. HALPIN: I think that industry would certainly be open to doing that, but I think that part of what industry would like to understand is what are the hurdles required to get a new indication. I think that leveraging existing data in any way that we can is very helpful in terms of not recreating the wheel or having to do something again from scratch. So I think they would be interested in

that, and in terms of trying to use as appropriate, the information they already do know about the product.

DR. LoCICERO: Yes, Dr. Li.

DR. LI: I just want to throw in, you know, get back on my soapbox again for basic research. You know, part of the difficulty here is we don't have basic information. If we knew what the tissue response was in the cheek versus some other area and the tissue response we know was the same, given a certain set of conditions then, in fact, you would not have to test in every single place. But in the absence of knowing these basic science details, I don't know how else to be safe other than to just retest it each time so that the carrot for doing the research is a rather big one, if you can ever get to that endpoint.

DR. LoCICERO: Dr. Newburger.

DR. NEWBURGER: I think that the pre-jowl sulcus is going to behave in a similar fashion to the nasolabial fold.

UNIDENTIFIED SPEAKER: Which --

DR. NEWBURGER: I think that this area is going to behave similarly to this area in terms of what caused those folds in the first place, and I

think it would be analogous in those areas. I don't think that they're analogous to the tear trough. I don't think that they're analogous to the perioral area and I don't think that they're analogous to the malar or sub-malar areas.

DR. LoCICERO: Other comments?

(No response.)

DR. LoCICERO: I don't think we can go any further on this question, Mr. Melkerson.

MR. MELKERSON: Thank you.

DR. DANG: The next questions has several parts. I'm going to read through all the parts and I will leave it to the Panel to decide which parts they would like to answer first.

In design of clinical studies for these new indications for tissue augmentation and recontouring, what safety and effectiveness endpoints, sort of in general I guess, would you recommend should be considered?

What are some clinical issues, both short and long term, which would need to be addressed? Some examples might be related to device migration, local tissue response and chronic inflammatory response.

What would be the most appropriate control?

Should FDA consider controls that are accepted as current standard of care? A specific example would be for lip augmentation, what treatment could be considered as standard of care and thus possibly considered as a possible control?

And when there is a potential for a larger volume and/or repeated objections of dermal fillers, over a relatively short period of time, such as less than six months, would acute and long-term systemic toxicity studies be warranted?

DR. LoCICERO: Okay. This is kind of a recapitulation of the day here. In terms of safety and effectiveness endpoints, does anybody have anything additional to add to what we've discussed so far? Dr. McGrath.

DR. McGRATH: Only that I think that this is a very complex question because I think there's going to be, each of those sub-questions will have an answer for each of the procedures. So let's just take hand volume restoration. I mean your safety and effective endpoints may be very different because you're going to be talking about, you know, motion and tendons and all different types of different pain, longevity because of the high degree of motion that you don't have in other parts of the body. So

you're going to be having very different both efficacy and safety endpoints. And I think for each of those things, you could do it. So I would find this a very difficult question to answer globally.

DR. LoCICERO: Mr. Melkerson.

MR. MELKERSON: To help foster the discussion, since it's difficult to answer globally, maybe picking some of the higher volume indications that have been reported or considered with augmentation, hand, cheek augmentation, maybe talking each one as a separate entity and is that a way to kind of walk through these questions.

DR. LoCICERO: Do we have another day? It's going to be a little bit difficult for us to go through all of these, but Dr. Burke, you can start.

DR. BURKE: I was just going to say not only are these different anatomic sites, different volumes of material being put in, but these special things, the lips, the hands, are incredibly technique dependent and, you know, no one would just go in and do it without very careful thought and anyone going in to do it would usually try to find a colleague who would have already done it.

And these will become more and more common but they're not the most common ways of using

implants in large, large populations at this time.

DR. LoCICERO: Okay. Dr. Olding.

DR. OLDING: Just to make a global -- I do want to make a global comment about those. All of them except maybe the hand volume restoration but probably it, too. It's more than just correcting a fold or a wrinkle. It really is I think more a global aesthetic appearance, and so I think the patient satisfaction scales are going to be very important in looking at these on its individual. That's why Dr. Pusic's material would certainly be of value in evaluating these more so than nasolabial folds and marionette lines.

DR. BURKE: But all of this having been said, there are areas that are incredibly sensitive like the under eye area, the base of the nose and the glabellar area. These are areas where there are potential serious side effects. So those again should be evaluated very differently, and technique and the type of filler are very important, and it's very variable the results you get with different fillers, even different molecular weights, different viscosities of the same filler.

DR. LoCICERO: Mr. Melkerson.

MR. MELKERSON: Your indulgence a little

further, and maybe these are more directed questions. Lip augmentation, one of the things that a lot of the wrinkle fillers to date have not looked at is, for lack of a better term I'll use function, but for other products where you're injecting materials, we look at, is there any impact on nerves sensitization? In other words, if somebody had a lip augmentation and you were unable to detect hot or cold, you actually may have further adverse events associated with it. If you're talking the hand, back of the hand, if you have loss of sensation in the hand, you have loss of function.

Are those the type of things that should be incorporated into these types of studies or maybe the general, the broad breast question is are there things that are unique to some of these locations that should be augmented in addition to having a global assessment? Are there things that we should be looking at, study designs that are looking more at, is there a functional implication to their use, you know, because I've heard more mobility, more issues of adverse events? In other words, are there particular things we should be looking at? And I've heard some of those.

DR. LoCICERO: So this brings up an

interesting issue. I read a lot of journals but I'm not really reading the aesthetic journals at this point. So if we are going to consider areas like this, we really are talking about areas outside of the current indications and there must be publications that address this clinically in at least some sizable studies. Are those available for questions like this? And, should the FDA looking at what's been published as a guide for it? What secondary endpoints should they be looking at? Dr. McGrath.

DR. McGRATH: Well, I can answer that affirmatively. I mean if you look behind one of the tabs right here, there's a smattering of some of these papers. There's one specifically here on the hand. There's one specifically on the lip, and certainly in the published literature, there have been multiple supplements in different specialties in the journals on best practices for using the injectables in all of these locations but I think that for us to try to say we could come up with a couple of things today is kind of presumptuous because we really need to sit down and think very hard about this and pull the literature together and pull all the data in and really look at each anatomic

site. But I'd say, yes, if that was your question. Should different considerations be had? Yes.

DR. LoCICERO: So the Society of Thoracic Surgeons has a large database on cardiac surgery that approaches 2.5 million patients now over about 20 years, which is a very powerful database for looking at outcomes and helping to direct where research should be. So I suppose if Dr. Weiss actually had a database from his Society of a million injections already, that would certainly help you a lot.

So maybe again this is something that is important that the societies consider establishing databases where this kind of information can be kept and then presented to the FDA as an assist.

MR. MELKERSON: I'm going to push one more time and ask for your indulgence, and maybe I'll put it in direct question for things like lip augmentation and for hand augmentation. Should there be functional evaluations along with a cosmetic or cosmesis or global assessment, I guess is the short question? I mean those tend to be the questions in terms of pushback that we get in terms of when people come to talk to us about, well, it's just an aesthetic or cosmetic device. Why do you need to look at function? So maybe those are the types of

questions but those two particular questions come back to us all the time with these type of studies.

DR. LoCICERO: Dr. Newburger.

DR. NEWBURGER: I think function is a critically important issue in both the hand and the perioral area, and because of the unique anatomy in the perioral area, it's going to be much more vulnerable to a lot of problems, for example, with repeated injections and scarring that occurs.

Over time, as lips thin, the scarring will become much more evident. So what seems like just a minor issue when someone is, you know, in their early sixties may become very evident five, six years later as the lip volume continues to diminish.

Also, there is an issue where I've seen a number of people reporting sensory deficits with perioral injection, and I think that if you ask the right questions, at the outset, then you get the information you want. I think that's much better than going to a database which is perhaps in retrospect. People tend not to report their adverse events in publications or they're just dismissed as anecdotes. Most of the reports are on the how-tos and many of these are the equivalent of white papers that are sponsored by industry, but I think that the

key is to ask the right questions at the beginning. I think that's very important. It's the most mobile area of your face, and we need it to eat and talk and perform other functions.

DR. LoCICERO: Dr. Anderson.

DR. ANDERSON: Well, I think along with that, satisfaction is going to be directly related to functional deficits in those areas.

DR. NEWBURGER: One other addition please. It's important when dealing with enhancement to make sure that you're not just enlarging the lips but that you're preserving the anatomic landmarks. That is critically important. So there has to be a device that can maintain that precision in the area.

DR. LoCICERO: Dr. McGrath.

DR. McGRATH: I guess this is a question to you. We're talking now about off-label uses, and I guess my question is the following: why is the FDA asking about the design of clinical studies? Are we feeling that there is going to be an interest in doing clinical studies to, look at what are currently off-label uses to make them on-label uses or why are we venturing into these questions at this point?

MR. MELKERSON: Well, let me put it this way. I can acknowledge or not acknowledge people's

interest but things that have been reported in literature, there have been expressed interests by company, I won't say which ones, in looking at potentially expanding their indication base, and the questions that we're asking here are actually looking forward to what types of studies, what types of information would be there. So the purpose of a general topics is what have we learned from what we've seen and how to we apply that to new expansions, new materials and I think your conversations today have actually helped us in that endeavor.

DR. LoCICERO: So I think we can go onto the final question.

DR. DANG: And this is a repeat of an earlier question for new indications for use. If a post-approval study is recommended for potential new indications for use, please suggest the appropriate study design, comparison group, length of follow-up, validated assessment and safety and/or effectiveness endpoints.

DR. LoCICERO: Mr. Melkerson.

MR. MELKERSON: One thing I was just reminded from the staff behind me, one of the things that was embedded in all those questions was issues

of controls for things that currently there are no approved products for, suggestions and how to approach or consider those.

DR. LoCICERO: Okay. So we'll address that along with this question. So this is kind of a repeat but we've addressed this partially already in terms of new indications as we were discussing it before.

So the one thing we really haven't discussed is controls. So now we're talking about a product that is now currently on the market and the sponsor wants an additional indication and what would be an appropriate control for that in a new area? Would it be appropriate to consider the same product for its current indication as a control or would it be appropriate, is it going to be necessary for us to have a different control product?

(No response.)

MR. MELKERSON: Let me see if I can soften the question a little bit. One of the things that I thought I had heard from the Panel was in regards to a product already has an approved indication. So again, asking what is the question you're trying to answer. In other words, what is the response near bone, near other anatomical sites in a more mobile

areas? Are those the types of questions that you can do, and I heard discussions of different study design options of patient not treated for a while, placebo, or sham injections or using a product not necessarily on-label but currently available. We have used standard of care in other device areas. Are those things that would allow you to get a safety profile compared to what is being used?

DR. LoCICERO: So let's start with a ridiculous example. Dr. Burke, you're involved in a study and you get to see a picture of a patient who has the product injected in one spot, first is saline on the other side, three months afterwards. How long is it going to take you before you can figure out which side is which?

DR. BURKE: Probably two seconds.

DR. LoCICERO: Yeah, a microsecond, right?

DR. BURKE: Yeah.

DR. LoCICERO: So I'm concerned about the use of some products. Again, we've talked about trying to find a product that's similar and we heard comments before we started deliberating that this is somewhat of a difficult issue.

So now we're going to find a product that allows us to make comparisons that we can already

see. Mr. Halpin.

MR. HALPIN: If the product's already approved in a different indication, I'm going to throw out an attempt of a design, would it be appropriate? I think it might be to, in some situations, have the baseline of the patient act as a control. So rather than trying to compare it to a non-existent product or some other contrive to treatment, is to evaluate it on the basis of change from baseline, and use that as a starting point for a product we already have an approval in another indication.

DR. LoCICERO: Dr. Li. Comments about the comment.

DR. LI: I'm not quite sure what to do about the control issue because I think comparing it to the baseline of the patient, it seems like the injection site in many of the criteria are always going to be different. So I'm not sure. I guess I can't think that through quite yet. So maybe you can come back to me in a few minutes. I'm still working on it.

DR. LoCICERO: Dr. Gooley, any insights?

DR. GOOLEY: Well, I think the choice for a control could be very much case dependent. I think

in some cases using a baseline would be appropriate and perhaps in some other cases it may not be appropriate. I think this is another one of those questions that depends a lot on the product that's under investigation.

DR. LoCICERO: Since the product already has a safety profile, do we need to have the same rigor for the safety when it's going to go onto a new position? Yes.

DR. NEWBURGER: I think that we have to have safety addressed because you're going to be using, if you're doing a cheek augmentation, you're going to be using a vastly increased quantity of the material, and since we have many of these, we don't know how they're metabolized. We don't know what, if any, risk of toxicity or -- with such a large quantity is going to bring about. So I think that it can't be confined just to efficacy but there do have to be safety issues addressed.

DR. LoCICERO: Dr. Burke.

DR. BURKE: I think one control could be the possible maximum amount to inject in specific anatomic sites at one time, and also recommendations as to how frequent or infrequent those injections should be. So you could recommend a certain maximum

volume for a hand, a certain much lesser maximum volume for a lip or for a glabellar area, one treatment, and recommend that that treatment not be done more frequently than at least once a month.

So I think you could make some educated control limits in amount and frequency of injection for each specific anatomic site.

DR. LoCICERO: Dr. Bigby.

DR. BIGBY: I think that if sponsors are requesting approval for different anatomic locations, that what one does really has to be based on the product and the experience so far with the product. In terms of a control group, I'll go back to my general statement and that is that the most important outcome in this situation is patient satisfaction and quality of life issues, and I feel very strongly that the safety issue probably in terms of design of the study is the most important, and you have to make sure that you have a study that is powered sufficiently to exclude a frequency of adverse events that you find unacceptable and you have to define what those are, and the duration of the study has to have something to do with the length that the product is known to stay in and the sort of fairly vast if not systematically collected data you already have

about the products.

DR. LoCICERO: Additional comments?

(No response.)

DR. LoCICERO: Mr. Melkerson, I think we have kind of exhausted our brains here.

MR. MELKERSON: I'm thanking the Panel. It's a difficult discussion, but these are the discussions we have internally and also externally with sponsors. Thank you for exercising your brains.

DR. LoCICERO: Thank you. So the meeting of the General and Plastic Surgical Devices Panel is now adjourned until tomorrow morning again at 8:00 a.m.

(Whereupon, at 4:59 p.m., the meeting was adjourned, to reconvene the next day, Wednesday, November 19, 2008, at 8:00 a.m.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

GENERAL AND PLASTIC SURGERY DEVICES PANEL

November 18, 2008

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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Official Reporter

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947