report to you an adverse event called in by a user? How do you know that's accurate? The reason that I ask is you mentioned among the devices, there were 93 reports of malfunctions. Now, my practice and we have seven dermatologists, all of whom are very heavy users of injectable fillers. We have reported to manufacturers over 30 luer lock failures this year, and I would hate to think that there's only 60 plus individuals in the rest of the country who have reported this. So I question whether, in fact, that report gets to you from the manufacturer. What evidence do you have that there is compliance?

DR. LoCICERO: Yes, Mr. Melkerson.

MR. MELKERSON: May I ask that Douglas Wood, the Branch Chief of that group try to address this type of questioning. The presenters are familiar with the actual analysis of what was done. Policies and procedures would be Mr. Woods.

MR. WOOD: Good morning. My name is Doug Wood. I'm the Branch Chief of Product Evaluation Branch II, which is one of the two groups that review MDR analysis within the Food and Drug Administration. I'd like to address your question and Dr. Bigby's question and I believe it was Dr. Olding's question about some of the ways we do some of our reports, and

I'll start with yours, Dr. Newburger.

We do require, mandate by law, that manufacturers report adverse events to us through the MDR reporting system. These regulations are upheld through a number of ways, one of which is inspections. The manufacturer has the liberty, for lack of a better word, of determining whether a device adverse event is a malfunction, an injury or death report, or the infamous other. And they make their determination in their CAPA, which is corrective action and preventative maintenance system to determine whether or not they should report these reports to the FDA.

If they do not report them to the FDA, during the course of an inspection and the inspectors believe that they should be reporting these devices, they are cited in the FDA 483 form and the inspection investigation report and are mandated to report these device failures to us. So we unfortunately sometimes cannot enforce the reporting of these problems until after an inspection has taken place or until we are made aware of a lack of reporting.

DR. NEWBURGER: May I add one question then to that. When I was reviewing the -- website, I noticed in the case of certain devices that there was

an extraordinarily long delay between the time it was reported to the manufacturer and actually made it to be reported to FDA. So is this the kind of thing that would happen with the inspection or are they just behind?

MR. WOOD: That's the other half of your question I was about to answer, yes. In addition to whether or not a manufacturer does report, they are also required by law to report within a certain timeframe, and that is another thing that the inspectors, when they review a company's reporting they determine, did you meet the timeframe for those reports? And they can be cited for that as well.

MS. MIRSAIDI: But there is a time difference between the reports that gets to us and when it goes on the web. There's a delay between the time we read the reports and it gets to the website.

DR. NEWBURGER: I believe it's logged in though when you receive it.

MR. WOOD: That's correct.

DR. NEWBURGER: It's that incident to reporting it to them to logging it in, and it's awful long.

MR. WOOD: That's correct, and that is something that is addressed by our different

districts among the United States for reporting, and it is something that is observed when they do inspect.

Dr. Bigby, you asked a question about comparing the dermal filler reports to other reports that are submitted from other devices within the MDRs. And that unfortunately is a very difficult way to review our MDRs for a number of reasons.

For example, Dr. Newburger's comment just now about the delay in reporting or lack of reporting, many of the problems, such as luer lock connections and other connections, often don't get reported. Some devices, such as cardiac stents, which, you know, you have the stent, you have the failure, the device is ex-planted, it's reviewed, we can actually see those, hence comparing the one to the other is a very difficult way to compare. So the number of reports that are received based upon those type of situations, based upon the number of devices that are manufactured and are available to the public, also makes it difficult for us to make a comparison of that type when we're looking at reports and trying to find trend.

And, Dr. Olding, I believe you asked about reviewing adverse events on the professional service

websites?

DR. OLDING: Yes. We have a tracking system within plastic surgery that looks at the outcomes, and that includes things like injectables, and I just wonder how much communication or dialogue there is between you and those groups and that website.

MR. WOOD: Unfortunately, we cannot use those websites when reviewing adverse events. We are required to use adverse events that come from the user facility, the individual user themselves or the manufacturer. So we can't go to a website and take -- I realize that they come from the user on the website, but we're limited to having the users, right now to have the users report to us directly using the Form 3500, which is available to report adverse events to us.

DR. LoCICERO: We're running out of time here. We're going to get two more questions here. One quick one. The study design is presented by the sponsor to the FDA and approved for postmarket approval studies. Is that the way it works?

MS. SHOAIBI: Well, the study designs are usually developed by the sponsor and FDA --

DR. LoCICERO: That's all I want to know.

DR. ANDERSON: I'll be quick. I was wondering if data is collected regarding the level of training of the person who is doing the injecting when an adverse event is reported? In other words, is it a dermatologist, a plastic surgeon, a nurse, a medical assistant?

DR. WOOD: It is not required. Sometimes there -- I wish I had a copy of an adverse event form to show you, but in the form there is a narrative section, and sometimes, and I want to stress, sometimes information like that is provided, but that is not generally the rule.

DR. LoCICERO: Dr. Li.

DR. LI: My experience with this is that the weak link in this reporting system is not the manufacturer reporting to the FDA but the physicians reporting to somebody that there's an adverse event. In my own experience, that's done in an exceeding low period of the time.

For instance, in the program that I was familiar with, we would get 20 to 40 retrieved implants a week. As near as I could tell, for five or six years I was director, I don't think we put any of those as an adverse event.

So my question to you is, is the FDA doing

anything to basically provide some motivation or inspiration or some legal reasoning to actually improve that situation because in the absence of that connection, you could have the greatest manufacturer and FDA communication, and it would still be in a dismally low percentage of devices.

MR. WOOD: I completely agree with you, Dr. Li. That is one of the problems. As Nasrin pointed out in her presentation, our numerator data is woefully inefficient because of that very problem. One of the things that we're doing now is, in the program that was started in 2002, which right now it currently encompasses 350 hospitals, to try to get them to come forward and give us reports about events that are taking place. We have several other groups such as HeartNet and KidNet to help report specific areas there.

The only other thing we have currently that we're trying to promote is the request that physicians do report these adverse events when they happen. Right now the focus is so much on trying to get reports from hospital facilities and from the manufacturers that we don't have the funds or the resources to be able to do a great outreach to physicians and physicians' offices.

DR. LoCICERO: Mr. Melkerson.

MR. MELKERSON: Just a quick clarification or distinction actually. Post-approval studies are requirements or conditions of approval for Class 3 PMA type products, and there are actually some regulatory teeth behind actually doing and completing them. So for the PMA products, although they are required to also report under their MDR reporting systems, they are required to conduct post-approval studies. The 510(k) or premarket notification products, which are also reported, but it's not the subject of this meeting today but will be tomorrow, those also are voluntary.

So the distinction between what's a voluntary report for user facilities and the users themselves, versus the manufacturers which is required by mandate, but you've heard those limitations. So I wanted to keep that distinction in everybody's mind when we're talking about the two different postmarket looks at adverse event reporting or safety and effectiveness.

DR. LoCICERO: All right. One last question.

MR. HALPIN: I just wanted to ask very quickly, for the MDR I know that manufacturers are

required to report MDRs from the U.S. as well as from the experience outside the U.S. and given the off-label uses and the fact that other countries and other approvals may have labeling, do you have any idea from your reports how many of those MDRs are from outside the U.S. where they may have slightly different indications for you?

MR. WOOD: Actually I believe in Nasrin's talk she gave that information. Wasn't it like 17 percent?

MS. MIRSAIDI: 14.5 percent the reports came from --

MR. WOOD: Came from outside the United States.

MS. MIRSAIDI: -- other countries.

DR. LoCICERO: Okay. We'd like to thank all of the FDA speakers for their time and answers to the question. Thank you very much.

We are running a little bit behind now. So we are going to have a 10 minute break. Return at 11:15.

Thank you.

(Off the record.)

(On the record.)

DR. LoCICERO: Getting back to their seats.

The FDA is going to get their presentation ready to go, and I'm going to ask that we have an opportunity for just about five minutes, if there are any additional questions that the Panel came up with for the FDA presenters from this morning, we ran very tight, and there may have been some additional thoughts that came up while everybody took their break. So I'm just going to ask the Panelists again if they have any questions for the FDA. And we have one from Dr. Gooley.

DR. GOOLEY: Safety obviously was what these post-approval studies were designed to assess. I guess I'm wondering how -- and there were mention that the studies are not powered to low adverse event rates. First of all, I guess I'm not exactly sure what that means. Is there a benchmark that's considered sort of acceptable in terms of an adverse event rate? And, number two, how are these studies, how are the sample sizes set for these studies? Is the sample size set with a certain power in mind, with a certain objective in mind or --

MS. SHOAIBI: No, the sample sizes were selected based on feasibility, and they were not -- since these studies were not -- they did not have any particular sample size calculations done based on any

particular endpoint or any particular objective. There were mainly just descriptive studies to look at the safety and name the primarily adverse event that were mentioned.

And also the other issue is that because we really don't know the incidence or prevalence of some of these primary adverse events in the population with Fitzpatrick skin types IV-VI, that makes it even more difficult to design studies that would be able to detect any of these adverse events if they occur.

DR. LoCICERO: Dr. Li.

DR. LI: I had one question about the reporting of devices. Without specifying what particular device was reported on, could you tell us if the adverse events were distributed more or less evenly through different products, or is it possible that most of the adverse events came from one or two products?

MR. WOOD: Actually Nasrin did the actual analysis. So I'll let HR answer that particular question.

MS. MIRSAIDI: No, the adverse events came from about 9 to 10 manufacturers and different products. There were some differences between the adverse events in different brands, but they were

just locked together for this presentation.

DR. LI: I understand that, and I'm not trying to pick out a product. I'm just trying to get a sense for the distribution. So maybe my real question is, is there anyway -- I'm struggling to kind of calibrate the study --

MS. MIRSAIDI: I understand.

DR. LI: -- to something.

MS. MIRSAIDI: Yes.

DR. LI: And one possible way would be to calibrate the adverse event reporting in the study to what was reported, you know, through your watch systems. So is there any way to make that kind of a comparison or association to see if you're kind in the ballpark or not? For instance, if you have no adverse events in the study, but then you had many adverse events in the reporting system, then that would actually tell us something about the study.

MS. MIRSAIDI: I guess -- how can I put this?

DR. LI: The answer could be no, you know.

MR. WOOD: Actually because this is a general information Panel, we did not bring forward the names of the manufacturers or the companies that were reported in the MDRs. Unfortunately that does

kind of limit you on your ability to compare that to the ones you see in the post-approval studies, but we don't have that available today.

DR. LI: Okay. But it's something you looked at but --

MR. WOOD: It is something we looked at, and it is something we do look at when we do MDR analyses. As a matter of fact, when a post-approval study is done, the epidemiologist will typically ask the analyst within our branches to do a post-approval study on that particular device for that particular function.

DR. LI: Can you answer a yes or no or can't tell then? To the extent that you've looked, does the adverse events reporting from your watch system look anything like the adverse events reported in the study, postmarket study?

MR. WOOD: I can't really tell from what we've seen. Sorry.

DR. LI: Okay. Fine.

DR. LoCICERO: Dr. McGrath. I'm sorry. One more from Dr. Li.

DR. LI: One quick question on the study. These were followed at 12 and 24 weeks. Is that correct? As the evaluation points. Is that correct?

MS. SHOAIBI: For the three post-approval.

DR. LI: Right.

MS. SHOAIBI: For the three post-approval studies, all of them, the follow-up was 24 weeks, but for the premarket studies, the follow-up was between 12 weeks and 52 weeks.

DR. LI: Okay. My question is, is there any -- what do you know about the 24-week evaluation time period and the rate of degradation or changes of the particular filler?

MS. SHOAIBI: As you are well aware, they vary. Different compositions have different durability times, and also it may vary from person to person, but here unfortunately we're not talking about particular devices, and these studies did not really look at any degradation because the objective of these studies was just to look at mainly the primary adverse events and also some other adverse events. So even if degradation did occur which we cannot tell whether it did occur or not, they were not looked at, and that is not part of what the studies were designed to do or report.

DR. LI: Okay.

DR. LoCICERO: I sense a lot of opportunity here. Dr. McGrath.

DR. BURKE: I just had one small question. In the premarket study, the one nodule, do we know the skin type of that person, of that individual? There was one nodule in the premarket study, and do we know the skin type of that individual that had the one nodule?

MS. SHOAIBI: The skin type for the post -- are you talking about --

DR. BURKE: Premarket study.

MS. SHOAIBI: For the premarket study, I can't tell you at this point unfortunately whether it was Fitzpatrick I-III or IV-VI. But that particular study had between 11 and 20 percent of Fitzpatrick IV-VI. So I cannot answer that question at this point, but I can certainly find out if you are interested.

MR. MELKERSON: Are you referring to slide I guess 59 where it reports one nodule?

DR. BURKE: Yes.

MR. MELKERSON: That was actually, if I understand correct, was skin type IV-VI.

UNIDENTIFIED SPEAKER: --

MR. MELKERSON: So it couldn't. Okay.

DR. LoCICERO: Dr. McGrath has a question.

DR. McGRATH: I have sort of a general

question for the folks from Surveillance and Biometrics. And tell me if you think this is true, that the MDR system probably captures the most serious complications, and I guess I'm asking you, do you think the MDR system, it would seem that intuitively and just from experience, you would think that the more serious ones would end up being reported much more than the minor erythemas and temporary swellings, and do you have a sense that that, in fact, is true, not just from this product but from all the things you look at in the MDR system?

MR. WOOD: From the manufacturers that report and report diligently, I think your assessment is correct. Of course, there are some who do not, but for the vast majority of the manufacturers, I believe that the more serious adverse events that are reported are reported diligently and are reported accurately.

MS. MIRSAIDI: So we don't get MDRs for expected minor swelling, erythema, things like that. If they come to us as injury report, they should have some sort of medical or surgical intervention under injury reports. So I guess what you're saying is correct. We get those that are beyond regular,

normal, minor side effect of these products.

DR. LoCICERO: From that general question, it takes us right into general comments. So at this point, we're going to ask each of the Panel members to give us any general comments they have at this point, prior to looking at the questions for the FDA. We'll begin with Dr. Olding.

DR. OLDING: I think the Panel is presented with some difficult questions which we'll go over in a little bit, and I think they're made more difficult by the fact that we don't seem to have a really good handle on the numerator or the denominator, probably better on the denominator. And I think that we have to do something to improve the system for adverse events reporting.

I think both the FDA takes some responsibility in that as well as we have the physicians, and there has to be some easy manner to increase those numbers because our decision making, at least today, is for me going to be difficult because we don't have a handle on it, and the only other thing I would say is the post-approval studies, again, I was on some of the Panels that requested those post-approval studies, and I anticipated because I know there's a very strong discussion

between the manufacturer and the FDA, that I would not have heard today that the information that we could gather from those is somewhat limited because of the study design, and I would hope that we could address that in the future.

DR. LoCICERO: Dr. Newburger.

DR. NEWBURGER: I'm thrilled that we're meeting here today to have a chance to discuss these topics because it's a real attempt to accommodate the real world in terms of how these devices are used versus the very limited, very narrow situation that we're confronted with when we have the data presented in studies for PMAs.

That said, I'm also excited that we can brainstorm about how we can get a more accurate reflection of what's happening in the real world. FDA's hands are tied so greatly by the mandate that they have no authority to impact the practice of medicine, only the tools with which it is practiced. And this is a significant issue especially when many of the users of some of these tools are not physicians who will not be able to be reached by our professional organizations. But I'm really excited that we're doing this and that we will get some publicity as to the enormity of this issue.

DR. LoCICERO: Dr. Bigby.

DR. BIGBY: Actually I don't have any general comments. I'll just save them for the discussion of the questions.

DR. LoCICERO: Okay. Dr. McGrath.

DR. BURKE: Yes. I think it would be good to have really a kind of protocol that everyone follows the same protocol, and I'd encourage that it be as long a term study as possible but at least 52 weeks. Some of these fillers we know are still in the skin after three years according to the studies that we've read. So when a study is done, if it's possible to track patients longer, I mean because I think that's often a concern with the practicing physician and the importance of safety.

DR. LoCICERO: Dr. McGrath.

DR. McGRATH: At the moment, I have three thoughts. I'd just like to mention one is that from the discussion that we've already had about the MDR, it sounds like the incidence of very serious complications is low, but since that's the case, and since the incidence of all complications and adverse events are low, I think that the post-approval survey system is critical here and has to be supported and augmented.

My second thought is I think it's extremely relevant to separate out these products and to stratify them by whether absorbable or non-absorbable and start looking at this whole thing not as a unit but separate them by their duration and so forth, and other parameters, so we're talking about different things.

And lastly, I think someone else, and I love this term, since reporting is going to be key, it might help if the FDA, and I don't know what you have specifically on your post-approval survey or your MDA when people report, but a standardized narrative would be very helpful. Perhaps if the questions were asked about who the individual is who is doing the injection and other things were asked when an adverse event were being reported, maybe more information would be captured.

DR. LoCICERO: Okay. Dr. Walker.

DR. WALKER: Basically my comment is that I'm somewhat concerned at the amount of disconnect between the information that the FDA has presented and what's happening in the real world, and I just would like to, you know, address the idea that the FDA needs to make the reporting of these adverse effects much more -- make it some ease of use, more

of a simplification, amongst the using clinicians.

I personally have not had the experience of making a report to the FDA, but I've been told that it's quite arduous and time consuming, and there may be some other way to address that as well, make it simplified to get more of an accurate report from the general using public and the physicians who are out there using these products.

DR. LoCICERO: Dr. Anderson.

DR. ANDERSON: Well, I agree with several of the other observations today. However, I think it's important for us to be aware that we have three highly respected professional organizations who are offering to work with the FDA, and I think that's something that we need to keep in mind.

DR. LoCICERO: Dr. Li.

DR. LI: Well, I think the first issue of reporting is one that I actually haven't seen solved for any device in the United States. The only example I can think of anywhere in the world is the Swedish Registry for Joint Replacement, where that's basically a socialized medicine system and everybody that gets an implant is registered at the time of getting it with the government.

Short of that, I'm aware of any system that

actually could get the reporting percentage up, although I applaud the efforts of the professional organizations. At the moment, I just don't see how that's going to be improved.

And I guess my own comments to Dr. McGrath's comment is, we really have no idea what the number of adverse events are in these devices. If they really have 175,000 reports, just quick back of the envelope, I calculate that's something like 1/100th of a percent of all the devices that are implanted if you're going to take that as some example. So I just don't see a way forward in that.

And just quickly on the study, the study for me presented more questions than it did answers. It was kind of an arbitrary setting of patients. As Dr. Gooley pointed out, we're blinded to the device which means we're also blinded to the device variables. It's a single time evaluation, and then kind of worse yet, there's kind of no correlation of the results to any other previous report, either in the device reporting system or the premarket approval. So I'm kind of left with not exactly sure what to do with the information in the post-market study.

DR. LoCICERO: Dr. Gooley.

DR. GOOLEY: Well, I don't have very many comments. I'm a statistician. So I look at things from a statistical point of view, of course, but towards that end, I guess the one thing that I sort of wonder about is, as I mentioned before, how these studies are powered and whether or not there are enough patients studied to answer the questions that need to be answered.

Specifically safety if you're taking about low event rates for the more serious adverse events, I guess I would be concerned the studies of sizes of 100, 200, 300 patients would be sufficient to ensure that the study is "safe" and, of course, that means that that brings up what is safe? How does one define safe? But I'm sure everybody that's involved in these trials have thought long and hard about those issues. So I would just encourage, of course, to keep thinking of those issues and like I said, I am somewhat struck by the seemingly relatively small sample sizes for some of these studies.

DR. LoCICERO: The device manufacturers and the consumers are probably the most important people in terms of comments, and I've saved them for the last of the general comments. So, first, Ms. Rue.

MS. RUE: My concern is that since

physicians are not the only provider of this devices and what we're doing, is that although we do have some efforts going out to the consumers of what they need to ask, I think that we need to use all kinds of media that the consumers can know what questions they're to ask to whoever's providing the service for them in easy to understand language, and it really needs to be flooded so they get those things before they go into the provider, whether it be a physician or somebody else who may not have that information readily available to them.

DR. LoCICERO: Mr. Halpin.

MR. HALPIN: From a manufacturing point of view, anytime anyone complains to us, we're required to collect it by regulation. It goes into our complaint system. There's actually a predefined definition of when we would actually report something as a MDR and as you heard earlier from the FDA, they will actually come out and look at how well we're actually doing it. Given that 94 percent of what is in the MDR system is reported by manufacturers, I would think that we're actually doing a reasonably good job or being checked. However, that unless it's reported to us, we're not able to really forward it on and report it.

We also do trending internally as part of our quality system requirements and try to identify complaint trends as well as adverse event trends that may be changing over time.

With regard to post-approval studies, I think that from an industry perspective, any guidance we can get that would help us design these types of requirements into our pivotal studies, so that we're able to look at something like skin of color in a prospective way as part of our original trial design would be very helpful.

DR. LoCICERO: Thank you.

Okay. At this time, we'll focus on the discussion on the FDA questions. Copies of the questions are in the folders for each of the Panel members.

DR. DANG: So I will present each question, one by one, and open it up for discussion.

So the first question is related to the discussion on postmarket evaluation of adverse events. Current labeling for dermal fillers state that most adverse events are immediately noticeable and temporary. Please discuss the adequacy of the current labeling including whether labeling should be modified to include adverse events that may manifest

several weeks to several months after the initial injection or those adverse events that may take some time to resolve, such as scarring and necrosis.

And also, should labeling be modified to include such types of adverse events which were not observed during the clinical study premarket but are evident in postmarket adverse event reporting?

DR. LoCICERO: Thank you. Does anyone want to begin? Dr. Newburger.

DR. NEWBURGER: I think it would be very helpful to change the labeling so that it is a fluid situation. My understanding from drug labeling is that as adverse events and associations are reported after the period of approval, that they are then added into the drug insert, and it doesn't seem that we have the mechanism for that with the devices. Certainly, there are many adverse events that can develop two and three years after implantation of these devices. I've certainly observed patients where that has happened, where they will have been injected with an approved elsewhere, of course, and then will show up with very large nodules that have developed and biopsy characterizes these as granulomata which have developed in response to the material that had been injected.

So I think that it should be modified to include the late developing adverse events and should follow the CDER model.

Furthermore, the clinical studies of many of these products are so small whereas drug studies generally have a much more robust patient population. Also drug studies have generally a more defined endpoint that's the nature of the drug. So I think it's very important to be able to accommodate to what we see developing over time, especially with the longer-lived products.

The size of the studies are such that we really are missing the 1 in 1,000, 1 in 10,000 and 1 in 50,000 adverse events.

DR. LoCICERO: Dr. Anderson.

DR. ANDERSON: I think that since these products are primarily used on the patient's face, most of the patients who come into have this procedure done are coming in to look better, and if we know that a particular longer term adverse event such as scarring and necrosis can occur, I really think these patients should be informed of that possibility.

DR. LoCICERO: Dr. Burke.

DR. BURKE: I think since some potential

adverse effects might be years later, I think that we should what is the longest experience, I mean within the write up, it should say this material has been used for X number of years and these are the adverse events that have been reported as of this time. I mean specify exactly how many years experience is within the write up.

DR. LoCICERO: Let me see if I understand correctly. The wording might say over 7 years experience, these are the events that occur --

DR. BURKE: Yes.

DR. LoCICERO: -- after 3 months or something.

DR. BURKE: Yes, but we postulate that some of the long-term events might be years, many years later as in the case of silicone. So, it's nice to know that something has been used for 10 years or 15 years, and there are no adverse effects, and that's much stronger than something that has been used for one or two years for something that doesn't degrade biologically.

DR. LoCICERO: Okay. Dr. McGrath.

DR. McGRATH: I guess my comment's a question also. I think everyone probably will agree that the labeling should be modified to reflect what

we're learning further about the products but would the manufacturers label modifications be limited only to their individual product or should it be limited to their product as it falls into a class of products? And if the latter, then we'd have to define the classes, and again the thing I keep going back to is the absorbables and non-absorbables because length of time and all these things are going to be so dependent on which product we're talking about.

So I guess my question is I think the modification answer would have to be elaborated on even more about what that would include when the modifications are put on the label.

DR. LoCICERO: Dr. Bigby.

DR. BIGBY: I think this is almost a no-brainer question. I mean the current label is not adequate. The answer to the question about should it be modified to include these others things is yes, and should it include adverse events that weren't reported in trials? If you only have a trial of a couple of hundred people, that's not a trial. That's designed to define adverse events. So, yes, you should talk about things that came up in postmarketing.

The other thing to remember is, you know, what you put in the label here is not going to have that tremendous of an impact on utilization because these are highly popular procedures. People are making a lot of money doing them. So putting things in the label is not going to have -- I mean how much of an impact is that going to have anyway? So I think at a minimum you need to enforce the label so at least what is known about adverse events is included in the label.

DR. LoCICERO: Okay. Dr. Bigby mentioned the postmarket studies. Does everybody agree that that individual needs to appear in the label?

Everybody's shaking their heads.

Dr. Olding.

DR. OLDING: I think that it should, in fact, be included with the labels ultimately but as we've heard today, it depends upon the quality of the post-approval study and what you can glean from that. Currently, I wouldn't want to include this data because we've already been told that it's really not comparative.

DR. LoCICERO: Understood. Dr. McGrath, additional comment?

DR. McGRATH: And again, just in response

to your specific question, you're saying that everything in a composite that we've learned from all the postmarket surveys, should it go on the label? I would say, no, because again I think it's got to be stratified for the product because clearly we're seeing differences in the different products. So, you know, if something is bubbling up with one product and not with another, I don't think it should go on all the postmarket labels. I'm sorry. On all the labels.

DR. LoCICERO: On all the labels. I'd like some more discussion concerning the class of agents. If something came up in a non-absorbable, that has not been seen in an absorbable, and it's maybe with a particular product but it's a serious event, should that be something that's listed in the class of products in their insert?

DR. OLDING: I would divide it even further than just absorbables and non-absorbables but we have different class types. We have the hyaluronic acids. We have calcium hydroxylapatite, et cetera. We have silicone. Those are all different classes, and I know Mary would probably agree with me that each of those have their own potential complications and adverse effects and they should be stratified based

on those types.

DR. LoCICERO: Dr. Bigby.

DR. BIGBY: No, I mean I agree completely with Dr. McGrath about separating them into classes.

DR. LoCICERO: So who would we ask to define the classes? Is that going to be the FDA's job to classify for us? Dr. Olding.

DR. OLDING: I really like the idea that's been presented a couple of times today, the consensus conference. And I would hope that something like that would be very important in helping decide these sort of questions.

DR. LoCICERO: Dr. Newburger.

DR. NEWBURGER: I don't know whether it's actually fair to lump products that are even made from the same molecule in the same class because there may be different variations based on how cross-linking occurs or the shape of the molecule. We know that certain shapes are going to provoke immunologic reactions more than another, and I don't know that it would be actually appropriate to tar all products in the class with the same brush but that's something that could be looked at when the initial data come out.

DR. LoCICERO: Dr. Li.

DR. LI: Along a similar vein, not to make a problem harder, but it's not simply a matter of the chemical makeup or composition of the filler. For instance, the size of the particles or the dose response of the particles to different tissue types will be highly variable. In other words, small amounts of a highly active material is safer than, you know, large amounts of some other material that might have a lower actual biological activity. So it's not really so simple, that if you have material A, it's always better than material B. It just doesn't really work out that way.

And I think also the further complication would be the different tissues in the body. We know, for instance, polylactic acid has different cellular response, if I put it near the bone or if I put it in the cartilage, we know for sure that there are different tissue responses. So it becomes a very difficult thing, I think, to try to generally classify these devices, that if you're in this class, you're okay, and this class you're not because I'm willing to bet that every time you do that I can find a counter example.

DR. LoCICERO: So we may be making this more difficult, but I think we can all agree at this

point, Mr. Melkerson, that clearly adverse events that occur after PMA need to appear in the labeling and information concerning postmarket approval studies for that particular agent need to appear in the labeling. We are somewhat divided. I don't know if we need to vote because we're going to split regardless of what we do, but we need to communicate somewhat that groups of drugs may, groups of devices may have similar reactions. Mr. Halpin.

MR. HALPIN: I think this might be an opportunity where maybe working on a guidance document or something where to give industry who's the expert on their preclinical testing and how their product works as well as maybe their clinical trial data, the FDA has a lot of cross-product information and then academia has their experience with the product in using it.

A guidance document might be a good way to allow those three different sort of tensions to work themselves out in terms of what might be the best way to approach, how you classify, if you classify, HA dermal fillers, absorbable or non-absorbable and how you go about that.

DR. LoCICERO: So that's known as spreading the pain.

MR. HALPIN: Exactly.

DR. LoCICERO: Comments about guidance document for this. Anybody? Essentially what happens there is that that needs to be produced by the FDA and that it will be done in conjunction with other individuals. It takes a lot of work and time.

Mr. Melkerson, any comments?

MR. MELKERSON: I was just going to say in terms of a guidance document, there's actually ways for professional societies, industry groups or individuals to submit a proposed guidance to FDA. So an output from a consensus conference, even if FDA weren't involved, could be submitted for FDA's consideration through it's good guidance practices by process.

DR. LoCICERO: Other comments about question 1?

(No response.)

DR. LoCICERO: Mr. Melkerson, does this satisfy the FDA on question 1?

MR. MELKERSON: Yes, it does, and I'll just let you know that as a condition of approval, a post-approval study is actually required to update the labeling. Thank you.

DR. LoCICERO: Thank you.

DR. DANG: Okay. The next question is considering that dermal fillers, in general, are administered to healthy patients as an elective procedure for aesthetic improvement, should FDA's tolerance for mild to severe adverse events be different than for devices that are intended for treatment of disease? If so, does the Panel consider current FDA tolerance for serious adverse events be increased or decreased for aesthetic used products?

And going with that, what would be the most effective method or combination of methods for FDA communication to physicians as well as the public regarding the postmarket information collected by FDA, such as information on adverse events related to uses outside currently approved indication for use, delayed onset of adverse events as well as less frequent but severe or unexpected adverse events?

DR. LoCICERO: Thank you. We've got a lot of questions here, but this really I believe begins at least, to some extent, with the consumer.

Ms. Rue, do you have comments about this, particularly the first couple of questions?

MS. RUE: Well, when I was looking at this in reviewing all of it, my first concern was that this is pretty much an elective thing for self-

esteem. So what we tolerate for people that have pathology and diseases is different, and I feel that, first of all, we don't have a grasp really on what our adverse effects are, and we don't have a good a grasp as we do when we're working with something that's treating a disease.

So, therefore, I feel that we're not holding the companies to the same standard as far as the research on the adverse effects, and I think that we should have a tighter or a less tolerance for severe adverse effects and we shouldn't allow as many. And also the information, and I've said it before, that we have got to get the consumer this information to where they don't have to dig and dig and dig for the information. It needs to be very readily available so they know what these adverse effects are and what we tolerate.

DR. LoCICERO: Dr. Anderson, this really has a lot of psychological implications.

DR. ANDERSON: It does, and I've seen it for years in my practice. If a patient goes in for an elective procedure and all goes well, they're generally very happy and they go home happy and they live happily ever after.

However, if they go in for an elective

procedure and there are complications, particularly severe or serious complications, the psychological ramifications can be significant.

Therefore, I would agree with the consumer Panelist that we probably should have less tolerance for serious side effects. And I can even illustrate this in other situations. I work with transplant patients, and in our facility, we decided prior to the changes in live donation of liver transplants, we decided not to do live liver transplants because we would be a perfectly healthy individual at great danger.

So I don't think this is just a plastic and reconstructive surgery question. I don't think it's just a cosmetic question. I think it's an ethical and psychological, quality of life and medical question.

DR. LoCICERO: So how do we balance this against the long list of adverse events that scare the patient away from a potential procedure that has, you know, 90 percent or more success.

DR. ANDERSON: Well, I guess we would have to look at the severity of the adverse events, and it sounds to me like we need a better reporting system so that we can actually gather the number of adverse

events and how severe they are, and perhaps tolerate it if we report it adequately, if there are very few serious adverse events. But I think being able to tolerate more significant adverse events is not in the best interest of the patient from a psychological standpoint.

DR. LoCICERO: Additional -- Dr. McGrath.

DR. McGRATH: I thought this question was fairly specific and the first part was should the FDA's tolerance be different for these devices versus those intended for the treatment of disease. And to that, I would respond, because I'm blessed with some historical perspective, watching the FDA and being with the FDA over many years, that I think it always has been. I think that there is a recognition that there is a difference between illness and quality of life applications, and I think historically the FDA has walked this line for many years.

So when we get to the next part of the question, should the current tolerance be increased or decreased, to that I would answer neither. I think actually that tolerance is in equipoise at the moment pretty well, and I think that's why we're here talking about these things now.

DR. LoCICERO: Dr. Bigby.

DR. BIGBY: So my comments about question 2 are the following. It isn't at all clear to me what the FDA's tolerance is of these things. So I think you could go along way in sort of defining what is your tolerance because as has been mentioned, the actual rate of serious adverse events is relatively small. So what exactly is your tolerance for severe adverse events? You know, what level of adverse events is unacceptable? And, what level of study would we need to find out whether or not that frequency exists?

And then to the second question about communicating information about postmarketing events, I think you should start by doing a better analysis of what those events are and their frequency, and I can give you two examples. One would be to look at the adverse event rate by product, by specific product, and then you can report that adverse reactions are much higher for this group of drugs or this particular drug than others and then also adverse events per location. If you find that the adverse events are 100 times higher, if you inject around the eye, I think that's a worthwhile thing to report, but you have to analyze your data in that regard before you can report it.

DR. LoCICERO: Dr. Newburger.

DR. NEWBURGER: I think Dr. Bigby's comment about what the FDA tolerance is, is an excellent one. The only recalls that I recall were for devices that posed life threatening threats, and I'm not aware of anything other than psychologically life threatening events that have occurred with these fillers other than perhaps severe infection.

From the point of view of ethics, I think that the tolerance should be decreased because these are not devices which preserve the ability to walk or to keep a heart beating or to preserve one's vision.

But I have some comments about the most effective methods for communications to physicians regarding postmarket information. I think that a lot of this really should be also directed to the consumer because many of the injectors are not physicians or if they are supervised by physicians, it may be at a distance and they won't get the communiqués and there are a number of ways that that could be done, not the least of which would be to have one of the myriad of celebrates injured by improper filler use to be the spokesperson, and I can suggest half a dozen off the top of my head.

There is a network, I think it's the HPNN

network where FDA adverse events related to drugs is disseminated to the physicians on the web, and it's very easy to sign up, and then they keep sending you every alert possible from FDA which is why you might be disinclined to join, but if there was one separately that's available online just with a weekly update. I think that that would be a very good method across the board to reach those who are providers of this service. And, it's free.

DR. LoCICERO: Back to Dr. Bigby's comments, about location of injection. These products have some pretty specific indications and we know from some other reports and discussions today that injection closer to bone, for example, may result in a different type of reaction. That's really not the indication for the product. So how can the FDA make a statement concerning an adverse event that occurs not for the indication that's on the label?

DR. BIGBY: Are you directing that question to me?

DR. LoCICERO: Well, you opened the comment. So --

DR. BIGBY: You know, a product that is approved for an indication that becomes available in

the open market often gets used for other indications, and often those indications far exceed the use for the indicated application. For example, Thalidomide is approved erythema nodosum leprosum which there are very few cases of but it is used in hundreds of patients with other disorders, and I think that in that situation, one can talk about the adverse events when it's used for other indications and it has been done, especially if it's a serious adverse event like neuropathy, for example, or birth defects. So I don't see how this is a problem.

DR. LoCICERO: Dr. Li.

DR. LI: From the non-clinical aspect, I'll just pass on a thought. Maybe somebody else can comment. In question 1, we had a lot of discussion of where the reporting of adverse events leaves a lot to be desired. It's some small fraction probably of what actually occurs. Certainly if we had a full reporting system, it's unlikely that adverse events would decrease in percentage. So what we're reporting is some really kind of a tip of an iceberg kind of view of the adverse events.

Now, given that, it seems that it would do a disservice to that whole reporting system if we then downplay the importance of those adverse events.

In other words, if we had a higher tolerance for these adverse events for these dermal fillers, I'm not even sure then at that point why you were doing any kind of adverse event reporting at all, right, because we've just acknowledged that it's the underreporting of the actual events and severity.

So if you then dismiss them or lower their importance and have a higher tolerance, then I think it really kind of does a disservice to the potential harm it may be doing to the patients.

DR. LoCICERO: So let's be a little bit specific here. Labeling, for example, for drugs, we will have a study that lists all of the complications from a severe event, allergy, to diarrhea or whatever, and then after that, there's a list of, in addition, these things might occur, and it's just a list. Is that sort of what we're recommending? I'm seeing some heads shaking. Okay. So it would be a reason to list them. Dr. Li.

DR. LI: I guess I would say that would be a minimum. I agree with Dr. Bigby's comment that I'm not sure how much the labeling actually controls use. So I think that would be a minimum requirement.

I don't know if it's possible on the label, and maybe FDA can comment, you know, on some of these

things, you know, the vast majority of use is off label as Dr. Bigby indicated. So it's just kind of an odd device where by far the largest use appears to be off label. So I don't know if there could be stronger wording in the labeling that, you know, these are off-label uses or something like that. So it's an odd kind of labeling but it seems to be the elephant in the room that we all seem that we're stepping around.

DR. LoCICERO: I think we have some opportunity over the next few questions to get into that. What is our best way to disseminate this information to users of the product, not the consumers? Dr. McGrath.

DR. McGRATH: Well, looking at this previously, I listed four things, and I think that we're talking here about the adverse events and less frequent but severe and unexpected adverse events and so forth. Obviously the package insert, which we're talking about the labeling, the website I think, and I'm speaking of all the websites at this point, I think it should go into the manufacturer training materials because a lot of manufacturer have training modules and, of course, again that brings us back to the professional organizations, and what they can

contribute in terms of communication which is really going to be as key as what the manufacturers do with their training modules.

DR. LoCICERO: Dr. Anderson.

DR. ANDERSON: I would concur. I know that a lot of patients go to professional organization websites before having something like this done, and if there was a good consumer/patient piece to the website, that might be very useful.

DR. LoCICERO: Okay. Well, Mr. Melkerson, on these two questions, major questions, the Panel seems to agree that at a minimum, there should be a listing of the adverse events that occur and I don't know, we are not in a consensus as to the level of tolerance that that should be, but we are in consensus that wide dissemination of information should be accomplished by the variety of methods that have been discussed this morning, a whole list of those.

Does this satisfy the FDA on these two problems?

MR. MELKERSON: I believe it does but I will plant a seed for this afternoon's session. On the questions of tolerance, the current study designs generally are powered for effectiveness. So when

you're thinking about safety tolerance, take that into consideration when you're thinking about this afternoon's questions.

DR. LoCICERO: Okay.

DR. DANG: Thank you. The next question is related to the post-approval study data that we heard this morning.

Based on clinical experience and results of the post-approval studies, is there sufficient evidence to conclude that the evaluation of dermal fillers in patients with Fitzpatrick skin types I-III can be generalized to patients with Fitzpatrick skin types IV-VI. If yes, would such a conclusion be limited to only the filler materials that have been evaluated in these post approval studies or would this conclusion extend to new filler materials not previously approved by the FDA?

DR. LoCICERO: Maybe we can take this one on pretty quickly. Can I have a show of hands of those people who believe that this is true that we can generalize from one data on I-III that it's okay for types IV-VI? Does anybody agree with that?

I see no hands up.

So, Mr. Melkerson, does that answer question 4?

MR. MELKERSON: I believe it does.

DR. LoCICERO: Thank you.

DR. DANG: Okay. Thank you. Moving on. This is also related to Fitzpatrick skin types IV-VI. Should clinical evaluation of dermal fillers consider patients with Fitzpatrick skin types I-III and IV-VI as two distinct populations with potential to exhibit different safety profiles? If yes, please recommend approaches or strategies that would evaluate safety and/or effectiveness of dermal filler use in patients with Fitzpatrick skin types IV-VI such as premarket study or a post-approval study.

DR. LoCICERO: So we just said that the studies on the I-III don't work for the IV-VI group. So how are we going to address that issue in studies? Mr. Halpin.

MR. HALPIN: One of the things that I wanted to mention is that if you look at the studies that were done on IV-VI, and the studies that were done generally, they're not the same types of studies. So I think the struggle that everybody had was that you're trying to compare apples and oranges, and I think perhaps what we need to be doing is studying these, and they're the same protocol design, in order to see whether or not they're actually

different or not, and I think one of the manufacturers has actually done them.

So it may be that these two subgroups actually do react the same and that we just don't have visibility to the data in a way that would allow us to say that.

DR. LoCICERO: So one of the problems for the sponsors who presented data like this was recruitment. So how would industry address that issue?

MR. HALPIN: I think in some of the initial studies that were done, I believe the sponsors may not have been aware of the issue, and I think these are very fast and rolling studies in general. I think that a pre-awareness of what the issues are would allow the sponsor to understand how to enroll a study so that it's most effective for them but also covers the issue. I don't know if anyone else disagrees with that or not but --

DR. LoCICERO: Ms. Rue, a lot of this is driven by a consumer coming to a user, and is there a way to get the consumers to volunteer for additional studies? And this would have to be the darker skin individuals.

MS. RUE: Well, it seems that people are

always recruiting people to participate in some study or not, some research. I mean it's in every community, and I think some people do it just because of the interest in it, in helping to determine. Sometimes there's an enticement and I think that's what the industry needs, but you see advertisements all the time in communities that have research areas asking for people to participate, and I don't think this is any different.

DR. LoCICERO: So one of the questions embedded in this is, are these two different populations? And, we have a lot of experts here who deal with this sort of thing. Dr. Bigby.

DR. BIGBY: So I would say that the answer to that first question is no because actually if you actually look at the history of the Fitzpatrick scale, it was designed initially to determine a response to ultraviolet exposure and phototherapy. The initial effort only went to type III, and the IV-VI was an afterthought. If you actually looked at people's skin reactivity there is a large overlap in terms of skin color of people who have type I, II, II, IV, V and VI. If you look at their response to light, the range is quite broad and the bell curve is overlapped and there really isn't, I mean like

everybody has this idea that keloids and post-environmental pigmentary problems are much commoner the darker you get, and I think that that's a true based on many, many years of clinical experience but just because you have skin type II doesn't mean you're not going to form a keloid. So I think that the overlap is too great.

I think the thing to accomplish would be to know what the safety profile is among the people who get the product used, and I think the study design should just make sure you include that spectrum of people in adequate numbers.

DR. LoCICERO: Dr. Walker.

DR. WALKER: Yes. I would agree. I think that that's really the disadvantage of the information that we have before us is that we just don't have enough numbers, and I don't think going forward that that would be very difficult to change. I think in recruitment, making sure that there is a diversity among skin types and ethnic groups in any studies going forward would help to answer that question.

I also agree that there is no difference, and these are not two distinct populations. That's my own personal opinion, but we actually don't have

any scientific data to prove that.

DR. LoCICERO: Dr. Gooley.

DR. GOOLEY: Given the lack of data and the uncertainty of whether or not these are separate populations, it seems to me that the design of any studies, especially randomized studies, the randomization could be stratified on, on the Fitzpatrick score, to ensure that you didn't have a higher proportion of agents with higher Fitzpatrick scores in one arm relative to the other arm, that might impact the comparison of the two. That might also help to address the question of whether or not these populations are different for future studies.

DR. LoCICERO: Dr. Li.

DR. LI: I'll just put in my two cents on the materials issues, that again I think this has to be done on a material or product-by-product basis because the response to hydroxylapatite could be very different than a PLA or maybe even different molecular weights PLA. So I think it could be misleading to generally just use the skin types as a way to classify the response.

DR. LoCICERO: This might be something that could be modified by collaboration with societies.

DR. LI: Absolutely. So it's just not a

dose response but also perhaps a timing issue. Some of these things resorb at different rates. So in one product, 12 weeks may be a very appropriate follow-up time, but another one it actually might be 36 or 48 weeks. So I think to generalize the study at this point where we just don't know a lot of the basis information, could potentially, you know, lead us to wrong conclusions.

DR. LoCICERO: Mr. Halpin, this kind of presents a problem to industry and what's coming out from this Panel so far is let's get everybody in there but we may need to do it for different times and we need to stratify, et cetera.

That leaves the industry with not knowing who to go to, to develop these studies. Do you have any comments concerning --

MR. HALPIN: When you say who to go to, do you mean --

DR. LoCICERO: Well, we've just come up with the different ideas about how we should design the study. So right now industry works with FDA to develop these things. What are the resources that industry would like to see so that they're not missing some of these points?

MR. HALPIN: Well, I think that a guidance

document that would focus on clinical study design would be useful and the resources that I think we would want to have at the table would be industry, academia, and the FDA so that we have a consensus, so that as we move forward, we're actually moving together rather than separately and then coming back four years later and having everybody look at the issues associated with this.

I think another thing to think about with regard to Fitzpatrick skin type or skin color is studying the distributions as they actually appear, and I think that if you understudy a population, relative to what you're going to expose it to, that is cause for concern, but that doesn't necessarily mean you need to overstudy it either.

So I think maybe coming up with a consensus about what percentages are meaningful and appropriate for a clinical study, that everybody feels comfortable is representative.

DR. LoCICERO: So currently though, if a sponsor wants to produce a study, they go to academia and design something and bring it to the FDA and say is this okay? Are there additional players at the table that you would need to help design this study?

MR. HALPIN: I think typically on a study-

by-study basis, you would look at what available guidance is available, work with the clinical investigators who are helping you design the product and work with the FDA through the IDE process to develop a clinical trial design and move it through the FDA approval process. I would think that an individual study-by-study basis, to insist or enforce that other groups have to be involved may not be the best approach, that that may be too cumbersome. I think through the guidance document process, you can get consumer input, biomaterial input, academic input, FDA input, set a guidance document and then move on from there. That would allow preclinical issues, material testing issues or formulation issues all to be thought about and documented in a way which industry can then reasonably follow and know that there has been input from a number of different disciplines.

DR. LoCICERO: Dr. Li.

DR. LI: To make it not so impossible, I'll throw out as a suggestion, it might not be possible to write a guidance document that lays out every possible test combination for every possible material because I think we're nowhere near being able to do that, but a more workable solution might be to

generate a list of common questions that you'll want to have answered for each device, and then leave some latitude how you go about answering that question.

For instance, not specifying the specific follow-up time, but you might specify the manner in which you pick the specified time as a single example.

So it might be possible to write a guidance document as a start to list universal goals that all products should be able to answer this list of questions in a manner that's suitable for that device.

DR. LoCICERO: Mr. Melkerson, I think we're actually ready to answer this question but do you have a comment?

MR. MELKERSON: I just wanted to make sure we're touching base on a couple of points that may have been lost in the translation.

I understand your initial point with regard to is it generalized or two distinct populations, but one of the questions is, is it a premarket issue or is it a postmarket issue was embedded in that question and it was saying, if yes, I would ask that question, is it premarket or postmarket. If no, as well, and I wanted to make sure that got in as a

question, and also in terms of post-approval studies, those basically come from a recommendation from the Panel to approve with conditions to answer specific questions that were raised by that particular product, and then the study design is the responsibility of working with the postmarket surveillance EPI group and the sponsor to try to -- how do we answer those questions and design to answer those particular questions?

So a guidance document may be fine for the premarket. How do we go about testing these in the general to get an indication of proof or a premarket application but post-approval studies are generally based on what particular questions need to be addressed by that product. So I just wanted to make sure those were in your discussion points when you're talking about guidance.

It's hard to write a guidance for something that is dependent on the device and what questions come up.

DR. LoCICERO: So embedded in your embedded question, are there any products currently being evaluated in PMA, any dermal fillers out there, that are currently in trials that are just I-III.

MR. MELKERSON: The answer is no. We

actually encourage all and, in fact, one of your presenters actually described that they did not have a post-approval study to address issues IV-VI because they actually had a population insufficient to analyze those patients.

DR. LoCICERO: Okay. Additional comments? Yes.

MR. HALPIN: I just wanted to state that in looking at the second section of the question, where it talks about this is a pre or postmarket issue, you could handle it as either a pre or postmarket issue that if the sponsor's able to actually enroll enough patients according to guidance in a premarket, so then they wouldn't have a post-market approval study.

If they weren't, rather than kicking them off the market, you might just have a postmarket approval as a condition of study to continue the protocol and study patients in skin of color and that way you're not simply restricting people or taking them off the market because of the inability to enroll in a subtype.

DR. LoCICERO: So there are probably a couple of products out there being used now that have not had a post-market approval analysis. So Fitzpatrick type IV-VI, are we saying that those

products should be evaluated in a postmarket study? I see a lot of blank stars.

DR. LI: Well, again I mean we're missing something here but it seems to me, I'll speak for myself, that my knowledge of how these materials perform, especially as a function of skin type, in the short term, is not completely understood by me, and if there's some differences between them, I'm not sure where the differences come from.

So if I'm unsure of the results from the premarket study, I don't see how I could dismiss a postmarket study.

DR. LoCICERO: Other comments? Dr. Bigby.

DR. BIGBY: I have two comments. One is the answer to the question as you just asked, should be yes. If they haven't had adequate numbers, they should.

And then this is the one that I often ask at, you know, the CDER meetings, and that is has any device or injectable ever lost its approval because it did not adequately perform the postmarketing surveillance study? And the answer from the drug side, it seems to never have happened. So that asking for a postmarketing study seems to be a way to kind of sweep the problem under the table and be able

to talk about it for a long time but never to be able to do anything about it.

MR. MELKERSON: We'll, I'll put a caveat. The short answer is no product has been pulled but there are efforts to put, in terms of the presenter actually put up the website of actually trying to identify here is the status of the product, they are or they are not doing it. There are civil penalties and other things associated with it. So pulling it from the market may not be the regulatory authorities that we invoke to encourage those studies to be completed.

DR. LoCICERO: One final thing. There are some products, some devices out there that have PMA approval that had no postmarket study requirement. Are we suggesting that those be done voluntarily by the sponsor? Are we saying that those should be looked at again with the idea to do postmarket studies? Mr. Halpin.

MR. HALPIN: I'm going to comment that maybe we should be looking forward rather than looking backwards and that some of the products we may be talking about may have been improved a long, long time ago. So I'm not sure that it's necessary to go back and try and recover those products which

may have been improved a long time ago but look more towards what's happening how, where we're going forward. But that's just my opinion.

DR. LoCICERO: Are there other comments about that?

DR. WALKER: My only comment would be that moving forward I think just in terms of the adequate study design, including all skin types is important as well as looking at the duration and the actual mechanism of action of some of the newer longer lasting devices. Some of the older products were very short lived and even within the timeframe of their effectiveness, whatever the adverse events were associated with the product, also resolved by the product disappeared. That's no longer the case.

So the older products to me don't seem to be as much of an issue as some of the newer one to five year product duration issues that are about to come down into the marketplace.

DR. LoCICERO: Ms. Rue.

MS. RUE: I would think if we got better adverse reporting in general, then it would indicate whether that that would need to be done or not but since we don't have adequate adverse reporting, we don't know that.

DR. LoCICERO: Additional comments?

(No response.)

DR. LoCICERO: Mr. Melkerson, does this answer that question for you?

MR. MELKERSON: I think you've discussed the question to our satisfaction, yes.

DR. LoCICERO: Thank you.

DR. DANG: That concludes the morning session.

MR. MELKERSON: Wow.

DR. DANG: Well, I can't conclude it. You can conclude it, but as far as the questions, we're done. Sorry about that.

DR. LoCICERO: Okay. So we're just a little bit behind. We're doing very well.

So we're now going to break for lunch. We'll reconvene again in 45 minutes. We're going to make that 1:20. Please take any personal belongings that you might want at this time. The room is to be secured by the FDA staff during the lunch break. You will not be allowed back in the room until we reconvene. Thank you.

(Whereupon, a luncheon recess was taken.)

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

(1:32 p.m.)

DR. LoCICERO: -- finished pretty much on time. We're going to have the second open public hearing. The first speaker of the afternoon session is going to be Dr. Andrea Pusic. Is Dr. Pusic here? Dr. Pusic is coming up to the microphone now.

Again, we ask that you speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting.

Dr. Pusic.

DR. PUSIC: Thank you and good afternoon. I'm a reconstructive plastic surgeon at Memorial Sloan-Kettering Cancer Center. I completed my Master's in Epidemiology at Johns Hopkins in 1997, and since that time, the focus of my research has been in patient reported outcome measurement in plastic surgery.

As a disclosure, I'm one of the authors of the Breast-Q, a patient reported outcome measure that is owned by Memorial Sloan-Kettering Cancer Center. As an author, I receive a share of any licensed reviewed that Sloan-Kettering receives in their inventor sharing policy. My travel costs today are paid by Sloan-Kettering and the ASPS.

Over the past two decades in plastic surgery, we have become increasingly sophisticated in our techniques and in the products that we use. To support this progress, we, as surgeons, have become increasingly cognizant of the importance of patient reported outcomes research. We recognize that traditional outcomes, such as complications data and photo analysis remain important but taken alone simply fail to capture all key aspects of outcome.

We also recognize the importance of rigorous development and validation of patient reported outcome measures.

The FDA guidance document on patient reported outcome measurement development has been tremendously helpful to us in plastic surgery.

With grant support from the Plastic Surgery Education Foundation, we recently developed a new patient reported outcome measure for breast surgery patients. In developing this measure, we adhered very strictly to FDA recommendations. We incorporated patient input in every step of the process. Our conceptual framework was informed by extensive patient interviews and whenever possible, we maintained the exact wording used by patients for our questionnaire items.

Cognitive debriefing interviews then helped us to identify ambiguities, acceptability, readability and the appropriateness of the recall period.

We then combined these qualitative methods with quantitative work and field tested the questionnaire in over 2,000 patients in 5 centers in Canada and the U.S.

Through this rigorous development process, carefully following the FDA guidance, we were able to optimize the validity, reliability, responsiveness and very importantly the clinical relevance of this new outcome measure for breast surgery.

Our research group recently performed a systematic review of patient reported outcome measures for use among patients undergoing aesthetic procedures including dermal fillers. In our review, we identified nine measures. The quality of theses questionnaires was highly variable. Many have been developed based on expert opinion alone and none adequately assessed the impact of a negative sequelae or complications on a patient's quality of life.

Patient education was also not well addressed with no questionnaires assessing patient satisfaction with pre-procedural information or with

the instructions provided.

Based on this review, we determined that there is a need for a new goal standard patient reported outcome measure for facial aesthetic to evaluate satisfaction and health related quality of life among patients undergoing facial aesthetic procedures. Such a measure would facilitate comparison of techniques, quantification of positive effect, identification of patients most likely to benefit from procedures. It would also provide an important follow standard and a reference point for clinical trials, regulatory efforts and effectiveness studies.

With grant support from the Plastic Surgery Education Foundation, we've now begun development of this new measure, and we are now nearing the end of our first year of a three-year program of research.

In developing this new measure, our ultimate goal is to better understand the impact of aesthetic procedures and dermal fillers from the patient perspective and with this knowledge to improve patient safety and outcomes.

We believe that these tools will be of great value in assessing what we consider the most important of clinical outcomes, patient satisfaction

and quality of life. Thank you.

DR. LoCICERO: Thank you. Our next speaker is going to be Dr. Ira Lawrence.

DR. LAWRENCE: Thank you, Dr. LoCicero, and thank you for inviting me to present to the Panel.

My name is Ira Lawrence. I'm a board-certified internist and clinical immunologist and Senior Vice President of Research and Development and Regulatory Affairs at Medicis Pharmaceutical Company in Scottsdale, Arizona.

As the U.S. marketer of the world's leading hyaluronic acid dermal filler, Medicis has a long and well-established interest in insuring that the effectiveness and safety of this class of devices are based on the highest standards of clinical and scientific data available.

Restylane and Perlane are perhaps the most well-studied dermal fillers in the world. To date, there have been over 10 million patient injections worldwide with Restylane and Perlane with an excellent record of safety and effectiveness. The vast majority of the adverse events reported with our products were local events at the site of injection and were mild to moderate in severity and short in duration.

We currently maintain one of the largest dermal filler safety databases in the world and have used this database to provide up-to-date information on both the safety and the effectiveness of these products and our product labeling.

This has most recently been evidenced by our update to the product labeling which have included data on long-term effectiveness and safety of the use for periods of up to 18 months post-initial treatment including subsequent touch-up treatments with the devices.

We have also recently updated the potential adverse events section of the product labeling to provide information on additional adverse events that have been noted as part of our ongoing review of the postmarketing safety database.

We are fully committed to working closely with the FDA in meeting our post-approval commitments that have included the conduct of a study evaluating the safety and effectiveness of the device in patients with Fitzpatrick skin types IV-VI.

In addition, the long-term safety study I previously discussed included by design over 30 percent of the patients with Fitzpatrick skin types IV-VI.

As the Panel discussed this morning, each dermal fillers possesses unique characteristics in both their physical and chemical properties, as well as safety and effective parameters and, thus, we respectfully suggest that the Panel should consider similar rigor in conduction clinical studies and study design and that these should be applied universally to all dermal fillers approved by the Agency.

Given the unique aspects of each dermal filler, this information is critical to ensure that both physicians and patients are fully informed of the potential benefits and risks associated with the use of a specific dermal filler, in order to determine which product best suits their particular needs. This information should be updated with some frequency post-approval and should include all long-term safety data available to the manufacturer.

In addition, information related to the removal of the device, especially if such removal would require a surgical procedure, should be considered for inclusion in the label.

In the area of clinical study design, we would ask the FDA and the Panel to strongly consider the ability of manufacturers to extrapolate the data

collected from studies to correct nasolabial folds, to include additional facial folds and wrinkles, given the common anatomy and pathophysiology of these facial folds and wrinkles.

When considering study designs, it is important to remember that the patients who are being evaluated are often quite different from the usual population of patients who participate in clinical trials. They are seeking an immediate aesthetic benefit and thus may have a lower tolerance for a complex trial design which may either delay the achievement of that benefit or utilize a control treatment which provides suboptimal or even no aesthetic benefits. This may actually inhibit the ability of the study to collect important clinical data on safety and effectiveness in a timely manner.

In studies to evaluate new indications, which might include soft-tissue augmentation and recontouring of the face and other portions of the body, the FDA and the Panel should consider the value of utilizing a global aesthetic endpoint for effectiveness based on assessment by both the physician and the patient and which would include patient satisfaction measurements.

We believe this would more accurately

evaluate the overall aesthetic effect achieved rather than relying solely on quantitative scales which often do not adequately capture the aesthetic benefit sought by both the patient and the physician.

We appreciate the thoughtful proposals provided in Dr. Dang's presentation on potential new indications for dermal fillers and look forward to the Panel's discussions on these important points.

We have some concern, however, on the proposal for histologic evaluations using biopsy samples and given the fact that these are aesthetic devices. These devices are often used on the face or other areas where a scar which could result from a biopsy would pose an unacceptable risk to patients.

Medicis believes that when used properly by skilled healthcare professionals, dermal fillers offer patients significant benefits. It is essential, however, that all such devices are held in consistent, scientific and clinical standards for effectiveness and safety. We are fully committed to working closely with both the FDA and the appropriate professional societies to ensure that such standards are met in any studies involving our products.

The proposed consensus conference, as outlined by Drs. D'Amico, Redbord and Gold earlier

today, would seem to be an excellent start to such collaborative efforts. Thank you.

DR. LoCICERO: Thank you, Dr. Lawrence.

Our next speaker will be Dr. Robert Weiss.

DR. WEISS: Thank you for giving me the opportunity to represent the American Society for Dermatologic Surgery. I am the current President, and we are an organization that is comprised of board-certified dermatologists with an interest in dermatologic surgery, and we have more than 5,000 members. And we did a survey in 2007, and we found out that our members have performed over a million of the procedures utilizing various dermal fillers.

Numerous scientific studies concerning dermal fillers have appeared in our journal, which is Dermatologic Surgery.

The Society has developed consensus-based guidelines of care and physician statements related to them. Most of the statements I'm going to make today are based on our published literature with a little bit of infusion of my own personal experience as well as a very impromptu survey that I did this past weekend with about 50 of our members who teach filler procedures. So there is a bibliography available for your reference if you would like it but

being green, I didn't bring a stack of them today.

And I'm here to make some general remarks regarding the safety of dermal fillers in general without comment about any specific product.

In terms of disclosure, our Society does get a number of unrestricted educational grants from the various companies that make these devices. And, personally, I have participated in the CME programs and have received honoraria and we also do clinical research for Medicis, and I've been a speaker for Allergan, Medicis and ColBar, a division of Johnson and Johnson.

So in terms of the ASPS position, our position is that complications resulting from the use of dermal fillers, while are rare, are frequently caused by injection technique which is largely dependent on the experience of the person injecting and understanding aspects of facial anatomy, and therefore, we believe that many of these complications can be prevented by appropriate training, patient screening and product selection, of course, being appropriate for which part of the face that is being injected.

We believe that stronger safeguards should be put in place to ensure, like with the other

organizations, that thorough training of appropriate pre-trained practitioners included in anatomy, selection preparation and injection of the products is very, very important to minimize adverse tissue responses.

In the survey that I did over the weekend, I also got the same sense from our members that they felt in a similar way, and several of them commented on the incidence of side effects in type I-III skin versus IV-VI skin and most people's whose population comprised anywhere from 8 to 10 percent of type III-V for fillers, found that there was no difference in incidence in the side effects. So I found that interesting and it's certainly correlated with our own experience.

I think I've covered the main points that I wanted to make.

Oh, one other final point, that labeling for dermal fillers, especially with new fillers, with more permanent applications or much longer duration, where there may be side effects that manifest over weeks or months, we believe that those should be included in the labeling.

And that's my brief statement, and I'd be happy to answer any questions.

DR. LoCICERO: Thank you. Our next speaker is going to be Dr. Steven Fagien.

DR. FAGIEN: Mine will be in a PowerPoint presentation. Thank you. I appreciate addressing this group, Dr. LoCicero.

I'm in private practice in Boca Raton, Florida, and my personal practice is limited to aesthetic periorbital surgery and injectable agents for facial enhancement. I have a unique association with membership. I'm an oculoplastic surgeon, a member of ASOPRS but I'm also a member of the American Society of Dermatologic Surgery and the American Society of Aesthetic Plastic Surgery.

Even though I'm in private practice, I've been an educator most of my career and I believe in excellent outcomes in patient safety. I consult or am a clinical investigator for Allergan, BioForm, Medicis, and I've done investigational research for Allergan, Anaca (ph.), Medicis, Mentor and Sanofi-Aventis. I have no stock in Allergan.

My trip actually today was sponsored by Allergan. However, my presentation I believe represents all the companies here that provide dermal filler and perform clinical studies, and more importantly, I think this will represent the interest

of our patients.

As far as RCC preferences, the ideal situation or pivotal trials for new indications on currently approved products should be randomized and include a control arm. Both products evaluated should be similar. Products for new indication for fillers, there are currently no approved materials for intended future application such as lip augmentation or facial volume restoration. And as we heard from several of the speakers, our patients are asking for lip augmentation. They're asking for facial volume restoration, and we need to address this.

Limited randomized clinical controlled studies showing safety and efficacy, however, of fat injection as again mentioned is very limited.

The recommendations have been that there's non-treatment statistical controls with either a delay of treatment or unrelated control group as the patient has his own control, the possibility of a sham or saline as a control. Saline as a control may be immediately or soon obvious, however, for both the evaluator and the subject, which can add bias to the study. Adverse events will inherently be biased against study products if the control won't be

related to the procedure or technique and not due to the product itself, and it may raise some ethical questions at some institutions. And then today we'll talk about the argument against autologous fat transfer, being taking fat from one part of the body and injecting it into areas of the face as a control.

Why autologous fat? Well, some people consider it an ideal facial filler, but I will tell you it is not a dermal filler. It is meant to be placed in the subcutaneous space. Problems other with the use of autologous fat injection as a control, as it raises many concerns such as the limited access to physicians who currently perform these injections, enrollment difficulties which we'll get into. It requires sophisticated apparatus for facial augmentation with fat variable and fat procurement. There's so many variables including processing injection technique, the reliability of results. Is it required to have a sterile environment? Some injectors actually use general anesthesia. There's survivability and degradation of injected fat, donor site morbidity. So there's so many issues that we all think about, these will be entered into a clinical study if this is used as a comparator and then concerns with study design.

Now, ASPS recently published that actually fat injections are declining at a rate of 12 percent a year probably because better products are becoming available that are off the shelf. Due to the complexities of autologous fat, in fact, not all dermatologists or plastic surgeons perform these procedures, and we have seen that there's a growing rate of HAs unlike a declining rate of injecting fat, a significantly increased ASPS reports 35 percent growth rate.

We expect, although a small issue, that with a trial using fat as a comparator, it will be waited possibly towards plastic surgeons being the more frequent injectors of autologous fat.

Some enroll concernments include the fact that we're introducing a secondary procedure to harvest fat, and that may deter patients from enrolling in the studies. They are more likely to exit the group. They could opt just to not be involved in the study and use HA as an off-label use for these applications. Many patients are seeking, as mentioned, immediate gratification, and this will obviously delay their result and many may not accept the risk of the procedure or the secondary procedure required to procure fat.

There's so many variables, I won't go into every single one, but there's no standard method of fat injection, whether you're injecting the lip or the mid-face or the lower face. Harvesting is across the board so variable, the injectors, the method of anesthesia, where they harvest fat from, the cannulas that are used, irrigation solutions, timing from injection after procurement, the quality of the fats variables. Some patients have excellent fat. It has very low survivability. The age of the patient and the medical history may have an impact on that. The quality of the harvest fat depends also on what areas are used as a donor site.

Processing and storage is quite variable, how the material is watched, centrifuged, filtered, manipulation of it, adding growth factors or reagents to enhance the viability of the fat. The injection apparatus as I mentioned is very complicated. The needle size used to inject, the gauge, reusable needles, disposable needles, length of the needle, types of syringes, the volume of the syringe, the injection plan of delivery of the fat.

So, again, as I mention over and over, the immense amount of variables using fat as a comparator.

Finally, there's no significant inherent variabilities in the outcomes in autologous fat versus synthetic or manufactured filling agents since HAs for the reason for failure for HAs has to do more with technique. However, with fat, again as mentioned, with so many variables, the reason it is quite variable is it's a living cell. It basically requires a blood supply unlike these other agents. Requiring this blood supply is also dependent on many factors including technique, is there bleeding, is there possible infection or contamination, and they're biodegraded completely different. We know that pathways of biodegradation of hyaluronic acid.

Fat is a living cell. Once it's injected, theoretically it should stay for life. The other concerns we have is fat actually can grow as the patient gains weight. So you inject certain areas, the fat survives, and we can see five years later when they gain 100 pounds that that fat in that area may be altered significantly.

There are some inconsistencies with fat that again are related with HA basically dependent on the technique.

There's blinding difficulties. Obviously the patient would know if they've got a harvest for

fat or an injected hyaluronic acid. Scheduling difficulties, the timing, when we see these patients after injection is typically different. There's a lot of edema and so forth and some morbidity associated with the fat injections. So there's scheduling differences will be a problem.

Injection technique again, we typically overcorrect. With HAs, we typically treat to optimal correction. With fat, usually anticipating fat non-survival, patients are typically overcorrected and that may skew the results.

Adverse events, most of the clinical studies that we performed, the adverse events with the comparator, the agent that has already been established and approved, typically is less than the agent that is in the trial, and this is because those injectors have less experience with the agents that are used in the trial and more familiar with the agents available.

I will promise you that using autologous fat as a comparator, you will see more AEs with fat than you will with the agent that you're trying to get approval for.

So, in conclusion, it's my personal opinion and that of many others that the best control for the

new filler applications as suggested maybe a non-treatment control group. Due to limited physicians, patient preferences, variability to the process and study design concerned, autologous fat in my opinion is a suboptimal control. Thank you.

DR. LoCICERO: Thank you, Dr. Fagien. Our final scheduled speaker is Dr. Diana Zuckerman.

DR. ZUCKERMAN: Thank you. I'm Dr. Diana Zuckerman. I'm President of the National Research Center for Women and Families, and I'm delighted to be here to speak on behalf of our non-profit research and education center which does not accept funding from companies that make medical products. So I have no conflicts of interest.

Our Center is dedicated to improving the health and safety of adults and children, and we do that by scrutinizing medical and scientific research, explaining it and determining what is known and not known about specific treatments and comparing safety and effectiveness.

I'm also a Fellow at the Center for Bioethics at the University of Pennsylvania and a board member for two non-profit organizations that are focused on improving resources for the FDA.

My doctorate is in psychology. My post-doc

is in epidemiology. So I can speak to both the scientific and psychological issues here today, and I was on the faculty at Vassar and Yale and a researcher at Harvard and have worked for the last 25 years in the Congress, the White House, and non-profit organizations on health policy issues.

Concerns expressed today are consistent with the articles that have been published in medical journals and the calls that our center has received for many patients who've used dermal fillers. We know that some people are having serious unexpected adverse reactions.

The FDA has approved these products based on small, short-term studies, and so it's not surprising that these adverse reactions are not known initially when the products were approved.

And as you've already said, the products were approved based primarily on white patients, and we know that there can be differences due to pigmentation differences in the skin, and I think the big issue here is that this should not be a postmarket question. These products should have been studied on people with diverse skin types before it was approved, and we shouldn't be waiting until afterwards, but if postmarket studies have been

required, as they have been, they should have been well designed, well done and should be able to answer the questions that were asked, and if postmarket studies don't fulfill those requirements, the product should be removed from the market, or there should be large warnings about the limited information about their use for people of color.

It's the FDA's job and your job as the FDA Advisory Panel to determine whether these products are being studied in a way to prove them safe and effective and whether they are proven safe and effective.

And since these products have cosmetic benefits, not medical ones, we need to take all these adverse reaction reports very seriously. And even the cosmetic adverse reactions have to be taken seriously because we know that patients don't want to get rid of wrinkles and end up with large lumps on their face instead.

Unfortunately, the FDA has been approving these products for market based on very small, sometimes poorly designed studies. The FDA standards have been lower than the standards for life saving medical products when, in fact, they should be higher. The FDA should be requiring better studies

since these products have only relatively minor cosmetic benefits but potentially lethal or life changing risks. And I can say that because our center has received calls from numerous patients who have been harmed particularly by the permanent fillers such as ArteFill and silicone. I know you're not talking about silicone today, but these permanent fillers can have very long lasting, disastrous results, and I actually got an e-mail this morning from a mother whose son is basically hiding out in his home, no longer willing to go out in public, growing a beard and hoping that some of what he calls disfigurements resulting from ArteFill will not be so noticeable if he grows a beard. Obviously most people using these products are women and they don't have that option, but even for this patient, it's a very devastating experience and particularly because he blames himself for having been so vain as to have used this product to begin with for some very minor wrinkles and ended up with a face that no longer looks like his face and that looks asymmetrical and unusually basically abnormal he says.

So I hope that there are doctors on the Panel. I have heard some discussion today of experiences that you've had with patients. I know

that we're hearing from patients and most of the patients we hear from have not reported their adverse reactions to the FDA and unfortunately their doctors haven't either.

The biggest weakness of the approval process used for these products is that the FDA has relied on studies of patients who were treated only once or twice or maybe three times and usually studied for a year or less. But we know that these patients are using these products many times, sometimes every six months or so for the absorbable products, and that they can continue their use for many years and yet they have not been studied that way.

As FDA's MOD database indicates, allergies and cosmetic problems can occur later after two or three injections, sometimes years later.

For permanent fillers, we've heard about lumps the size of cherries, sometimes even ping pong balls on patients' faces developing years later. So, although these products clearly have some benefits, the question is do they outweigh the risks and if they do outweigh the risks for some products, do they outweigh the risks for all of these products. I'm disappointed that the FDA has not been willing to

talk about the postmarket problems of specific fillers and instead are talking about all of them. This issue has been raised already today, and I share that concern because consumers and patients deserve to have this information. Some of these products don't have a lot of adverse reactions and some of them do. And how are we going to help patients make appropriate decisions for themselves without providing that information?

And the last thing I want to mention is that in the approval of these products, there has been a reliance on approving the products relatively quickly and relying on postmarket studies and postmarket surveillance to find out what's really going to go on in the real world with real patients.

I have spoken with the FDA Commissioner personally and also heard him publicly state that the FDA's postmarket program does not work. It's terribly under funded, under resourced, and because of the data not being analyzed automatically, they don't have the proper computer software or hardware to do that, the system is broken. It will take years to fix it, and it is being fixed. They are spending millions of dollars to fix the system, but currently if doctors reported more adverse reactions, the FDA

could not handle the load of that because they already can't handle the load they have.

I know that the FDA officials here probably are not in a position to be talking about that today, but it has been stated publicly as I said by the FDA Commissioner and other officials.

So when Advisory Panels like this one depend on that postmarket required study or postmarket adverse reaction reporting, it just doesn't work. It's not going to work. We have to shift that responsibility of approving safety and effectiveness prior to approval, not afterwards.

Thank you very much for the opportunity to testify, and I have been working on these issues for any years and would be glad to answer any questions.

DR. LoCICERO: Thank you, Dr. Zuckerman. This concludes the scheduled speakers. Is there anyone else in the audience who wishes to address the Panel?

(No response.)

DR. LoCICERO: I see no one else wishing to address the Panel at this time. So I'd like to ask the Panel if they have any questions for the speakers. Dr. Li.

DR. LI: I just have a quick question for I

believe it's Dr. Lawrence. You said you were developing a large database to track your product. Is that correct?

DR. LAWRENCE: We actually have an ongoing database to track our worldwide experience with the product, that's correct.

DR. LI: Could you give us any indication of how many implants you're actually tracking versus the number of units you're selling?

DR. LAWRENCE: I don't have that information at my fingertip. I can certainly provide it to the Agency as a follow-up.

DR. LI: Is it a big number or a small number?

DR. LAWRENCE: It's a fairly large number that we track, yes, that is correct.

DR. LI: And you get 10 percent, 20 percent, 50 percent?

DR. LAWRENCE: I don't know that I can give that answer.

DR. LI: Okay.

DR. LAWRENCE: I don't have the exact number. I'm sorry about that.

DR. LI: Okay. Thank you.

DR. LoCICERO: Dr. McGrath.

DR. McGRATH: I had two questions. One for Steve Fagien. You spoke about using saline on autologous fat. How about using some other sort of injectable product? Do you think there's enough similarity that for instance if you were looking at a HA that you should use another HA as a control or why didn't you get into that discussion?

DR. FAGIEN: Well, one is that there's no approved agent still for use in cheeks or lips. So you would have to use a substance that would be acceptable like saline. The reason fat was suggested because it's not regulated, and the other option is to use something that would be acceptable to the Agency, however, is not approved. That would be another option but the fact that if we want to stick by the guidelines of having a comparator that is either FDA approved for that specific facial region, we're at a loss and I think once one agent gets approved, the next one will be very easy. We're here at the transition where we really don't have that. So that's why we're offering, you know, the options, and the one that I mentioned is the one that we think might be the best and the simplest one to use, but there are others, and sham saline is certainly one of them.

I think interestingly we talk about complications of fillers and I still find, and I've talked with Dr. McGrath, the problems are typically proximal to the syringe and less have to do with the product itself. So --

DR. LoCICERO: Dr. Anderson.

DR. ANDERSON: I had a question for Dr. Pusic. I wanted to know how close you are to the completion of a satisfaction questionnaire.

DR. PUSIC: We're probably still about 18 months to 2 years away. Currently, we're doing our qualitative work. So we're still interviewing patients and generating items for the questionnaire.

DR. LoCICERO: Dr. McGrath, you had a follow-up?

DR. McGRATH: Yeah, I had two questions for Dr. Lawrence. You commented about focus on the specificity of the filler and then you said shortly thereafter we're talking about the importance of long-term follow-up data. Would you predicate the length of that long-term follow-up on the specificity of the filler and how would you suggest that be done? That was my first question.

And then I want to take a second after that and ask you about your comment about extending the

data from the nasolabial folds to the other facial folds.

DR. LAWRENCE: Certainly. To your first point, Dr. McGrath, I believe that, in fact, it does need to be demonstrated or that long-term safety needs to be demonstrated in part based on the longevity of the effectiveness of the device. So I think it was discussed earlier by other members of the Panel that each device or each set of devices may differ with regard to the duration of their effectiveness, and I think that is the appropriate manner to follow long-term safety at least as an initial cut. There are also other delayed type reactions that may occur even after the device has been resorbed. So I think that's something that we need to work out with the manufacturers and hopefully with the academic community and I think again that should be the subject of something, for example, as the consensus conference that has been suggested. I think it would be very valuable.

DR. McGRATH: So you could see these potentially extending beyond the period when biologically we assume the material has already been resorbed?

DR. LAWRENCE: I think it would be

something that would have to be discussed carefully but I think it may be something at least as a postmarketing study that might be of value.

DR. McGRATH: Thank you. And my second question had to do with extending the data for nasolabial folds to other facial folds and creases. Again, I assume you're making sort of a similarity between folds and folds but when you move into another fold, that might be one that has more blood vessels or might have more neurologic tissue there. So I'd like to hear your reasoning on this because when you make that move, you may be moving into a very different kind of geography.

DR. LAWRENCE: Well, I think the proposal was that the Panel should consider that as a possibility to broadly apply nasolabial folds for certain wrinkles and folds within the face. Obviously there are a variety of consideration that need to be taken that would include both the vascular supply, the neurologic supply as well as the location on the face. But we believe that there are some wrinkles, and we have spoken actually to the Agency about this that are broadly applicable, and we are hoping that that's something that the Panel may wish to discuss and evaluate whether, since one of the

challenges, of course, for the industry is the fact that the only validated scale is with the nasolabial fold and, in fact, we know that a large number of additional folds and wrinkles are, in fact, being treated by physicians and healthcare practitioners and we believe having some information on the label that it will allow us to both educate and appropriately collect postmarketing safety data as mentioned earlier, would be very important both for the safety and the effectiveness of the product, but also for the well being of the patients and the physicians.

DR. McGRATH: I don't mean to put you on the spot, but a final question. What, for example, would be another crease or wrinkle on the face that would be quite comparable to a nasolabial fold?

DR. LAWRENCE: Well, certainly we've considered areas such as the oral commissures, marionette lines, areas around the glabellar lines that might also be comparable or at least considered for broadening the applicability of the device.

DR. McGRATH: Thank you.

DR. LAWRENCE: Thank you.

DR. LoCICERO: I have a question for Dr. Weiss. You mentioned that you had over a million

procedures performed by your members. What sort of a database is this and what kind of data are you collecting?

DR. WEISS: These are surveys that we went out by e-mail on a regular basis, and usually we get about one out of four of the membership responding. Sometimes as high as up to 40 percent but these are not certified. These are estimates that people make based on their practices and, for example, our numbers at our office I can just go back to our computer database and look up from the encounter forms that have been entered into the software exactly how many syringes we have used of each and then we have all of the patient data. So that's why I can say with confidence, because I actually asked my office manager to do that this morning, that in our practice alone, we've done over -- it's like a little over 6,000 patients.

DR. LoCICERO: You don't have a Society database where this is stored?

DR. WEISS: We're relying on the estimates of people who are answering their e-mail and then doing it. Some may be more diligent like us and actually get numbers, and others can estimate based on the number of patients that they see per day and

the number of filler injections that they do per day.

DR. LoCICERO: Are there any other questions from the Panel?

(No response.)

DR. LoCICERO: Okay. Thank you very much. We will now hear from the FDA for the afternoon presentation. The first speaker will be Dr. Jiyoung Dang.

DR. DANG: I just wanted to remind the group that this afternoon's presentation from the FDA will be discussing clinical study design. Dr. Francis will be presenting on clinical study design for premarket approval of dermal fillers as far as what we have seen at the FDA, and we will continue on with a presentation on some clinical study considerations for potential new indications for use, and those will be followed by the presentation of FDA questions.

Dr. Francis is a Medical Officer in the Plastic and Reconstructive Surgery Branch, and she will be presenting a review of protocol designs.

DR. FRANCIS: Good afternoon. So my agenda today is to discuss approved protocol designs for dermal fillers to date, and again this is going to be a summary of the protocol designs. They will be

lumped together. The following slides again will compile and characterize all of the dermal filler protocols which have been approved by the FDA. And, in addition, I'll be addressing dermal filler protocol designs and analysis issues. They will again be non-device specific and I will not be presenting data from premarket studies.

So, in summary, at the beginning of the presentation, a summary of the study protocols for all approved dermal filler products, and basically to summarize them, they're to evaluate the safety and efficacy of study devices when used as dermal fillers in the nasolabial folds, in a range of moderate to severe facial wrinkles, facial folds, wrinkles, nasolabial folds and oral commissures, or the correction of soft tissue contour deficiencies.

And with regard to the protocol designs, dermal filler devices have been demonstrated to -- well, the plan was to demonstrate effectiveness and safety using predominantly randomized, controlled, multi-center clinical trials. The study designs included either a split face design or a standard design where one of the cohort of patients received a control device and the other cohort of patients received a study device.

Masking of patients would vary, either subjects being fully masked or partially masked. The investigators were either fully masked or unmasked, and expert panels were also employed and were always masked and they would use photographs for evaluation.

The evaluation ranged from live assessment to photographic assessment using the Fitzpatrick scales, FWS, or a six point validated wrinkle severity scale.

With regard to treatment plans, the injection depths varied from sub-dermis, deep or mid-dermis. There were also linear threading techniques used, serial punctual injections or a combination of the two, and also tunneling was used.

With regard to pain management, physicians have been either advised to assess the patient's need for pain management, or they were encouraged to use a standard of care. They were using topical or injectable anesthesia and after the injections, sometimes also cold compresses and other things could be the standard of care and some of the protocols actually did not make comment about pain management.

With regard to sample size, 117 to 191 subjects were enrolled in the studies and of those subjects, 115 to 185 subjects completed.

Sponsors are also asked to submit a justification for their specific injection depths and injection techniques in a manner which allows for collectible approval data for a given injection depth.

With regard to endpoints, the correlation of the nasolabial folds would have been compared to control, based on the blinded evaluations, live evaluations, the nasolabial fold severity score again using the Fitzpatrick or other scales such as the facial fold assessment scale. These would be done six months post-optimal correction visit. The statistical objective in this case was to determine the non-inferiority of the study device to the control.

Other endpoints include the ability to correct nasolabial folds at three months in comparison to control by an independent panel of blinded dermatologists.

Another endpoint was that blinded reviewers use the Lemperle Rating Scale at three months after the last touch up was applied via blinded, photographic assessments by board-certified physicians.

And another endpoint included an

independent expert review panel to assess the nasolabial fold severity score decrease over the post-treatment follow-up period. The endpoint measured the wrinkle filling but should be supported by, of course, other data which allow the sponsors to make conclusions with a variety of unbiased input from blinded panels, patients and other criteria which we'll discuss in the next slide.

So as a result, we're talking about the secondary implants and again this is a range of all of the implants from all of the summaries of all of the dermal filler protocols to date.

Subject satisfaction has often been used with overall treatment response, and this would measure anti-porcine collagen antibodies and comparison of the total volume of study device injected into the nasolabial fold in order to achieve optimal correction and this would be compared to a study group.

Other secondary endpoints include the investigator's visual assessment of each patient's nasolabial folds using a six-point scale and a qualitative assessment of the level of correction by the investigator and by the patient.

Secondary points also included blinded