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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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GENERAL AND PLASTIC SURGERY DEVICES PANEL

+ + +

November 19, 2008
8:00 a.m.

Marriott Gaithersburg Washingtonian Center
Salons C and D
9751 Washingtonian Boulevard
Gaithersburg, Maryland

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KAREN BURKE, M.D., Ph.D.	Consultant
TED GOOLEY, Ph.D.	Consultant
STEPHEN LI, Ph.D.	Consultant
MARY McGRATH, M.D.	Consultant
AMY NEWBURGER, M.D.	Consultant
ERIN WALKER, M.D.	Consultant
MICHAEL HALPIN	Industry Representative
KAREN RUE, R.N., M.B.A.	Consumer Representative
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RICHARD P. FELTEN, M.S.

PUBLIC SPEAKERS:

ROBERT WEISS, M.D., UltraShape

PATRICK MARTIN, LipoSonix, Inc.,
a division of Medicis, Inc.

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M E E T I N G

(8:02 a.m.)

DR. LoCICERO: Today we're going to start at 8:00, more or less. So I would like to call this meeting of the General and Plastic Surgery Devices Panel to order.

I'm Dr. Joseph LoCicero. I'm the Chairperson of this Panel. I am a general and thoracic surgeon by trade. I currently am the Director of Surgical Oncology at Maimonides Medical Center in Brooklyn. I've got a tremendous amount of experience with lasers and pioneered some of the indications in thoracic surgery.

If you haven't already done so, please sign the attendance sheets that are on the tables by the doors.

Dr. Lim, the Executive Secretary of the General and Plastic Surgery Devices Panel, will make some introductory remarks.

DR. LIM: Good morning, everyone.

I will now read the Conflict of Interest Statement for today's meeting.

The Food and Drug Administration is convening today's meeting of the General and Plastic Devices Panel of the Medical Devices Advisory

Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the Panel are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with the federal ethics and conflict of interest law covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act, are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular government

employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussions of today's meetings, members and consultants of this Panel who are special government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties and primary employment.

For today's agenda, the Panel will discuss and make recommendations on general issues related to the clinical trials of dermatologic and aesthetic devices. Specifically, the Panel will make recommendations on how to quantify the effects of a variety of different types of energy sources, such as light-based products, light-based combination devices, focused ultrasound, massagers combined with other energy modalities, cryogenic energy, radiofrequency ablation devices, on dermatologic conditions.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waiver has been issued in connection with this meeting. A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Michael Halpin is serving as the Industry Representative acting on behalf of all related industry and is employed by Genzyme Corporation.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which a FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue. Thank you.

Before turning the meeting back over to Dr. LoCicero, I would like to make a few general announcements.

Transcripts of today's meeting will be available from the Free State Court Reporting.

Brochures are on the table outside the meeting room.

Information on purchasing videos of today's meeting can also be found on the table outside the meeting room.

I would like to remind everyone that members of the public and press are not permitted around the Panel area, which is the area beyond the speaker's podium.

The press contact for today's meeting is Siobhan DeLancy. Is Siobhan here today? She'll probably show up later.

I would request that the reporters wait to speak to FDA officials until after the Panel meeting has concluded.

If you're presenting in the open public hearing session today and have not previously provided an electronic copy of your slide presentation to FDA, please bring your slide presentation to the AV table.

Finally, please silence your cell phones.

Thank you very much. Dr. LoCicero.

DR. LoCICERO: Good morning again. At this meeting, the Panel will discuss general issues concerning the clinical trials of dermatologic and aesthetic devices.

Before we begin, I'd like to ask our Panel members and the FDA staff seated at the table to introduce themselves. Please state your name, your area of expertise, your position and affiliation. We'll begin with Mr. Halpin.

MR. HALPIN: My name is Michael Halpin. I'm the Industry Rep, and I'm the Vice President of Regulatory Affairs with Genzyme Corporation.

MS. RUE: I'm Karen Rue. I'm the Consumer Representative. I'm with Griswold Special Care in Lafayette, Louisiana.

DR. WALKER: My name is Dr. Erin Walker. I'm in clinical practice in White Plains, New York. I'm a board-certified dermatologist.

DR. LI: Dr. Stephen Li. My area of expertise is the testing and research and development of biomedical materials, and I'm the President of Medical Device Testing and Innovations in Sarasota, Florida.

DR. GOOLEY: Ted Gooley. I'm a biostatistician from Fred Hutchinson Cancer Research Center and also and Affiliate Professor in the Department of Biostatistics from the University of Washington in Seattle.

DR. NEWBURGER: I'm Dr. Amy Newburger. I'm

a board-certified dermatologist, Director of Dermatology Consultants of Westchester in Scarsdale, New York. I teach at St. Luke's Roosevelt Hospital Medical Center. I teach dermatology residents there as voluntary faculty.

DR. OLDING: Michael Olding. I'm Chief of Plastic Surgery at George Washington University in Washington, D.C.

DR. BURKE: I'm Karen Burke. I'm a board-certified dermatologist that has a medical practice in New York City, and I do research and teach residents at Mt. Sinai Medical Center in New York.

DR. ANDERSON: Rebecca Anderson. I'm a health psychologist. My area of expertise is outcomes and quality of life and ethics. And I'm a professor in surgery, epidemiology, and psychiatry in behavioral medicine at the Medical College of Wisconsin in Milwaukee.

MR. MELKERSON: I'm Mark Melkerson. I'm the Division Director of the Division of General, Restorative and Neurological Devices, and the FDA Representative of the Panel.

DR. LoCICERO: Thank you. Dr. McGrath should be here soon. Dr. McGrath is a plastic surgeon at University of California, San Francisco.

We'll now proceed with the open public hearing portion of the meeting. Public attendees are given the opportunity to address the Panel to present data, information or views relevant to the meeting agenda.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of the meeting.

For example, this financial information may include a company's or a group's payment for your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have financial relationships. If you choose not to address this issue of financial relationships at the beginning of

your statement, it will not preclude you from speaking.

We have two public speakers today. I'd like to go over the process to ensure a smooth transition from one speaker to another. After introduction, please approach the podium. When you begin to speak, the green light will appear at the podium. A yellow light will appear when you have one minute remaining. At the end of 10 minutes, a red light will appear and your presentation should be completed.

The Panel will be given an opportunity to ask questions of the public presenters at the conclusion of the open public hearing. If recognized by a Panel member, please approach the podium to answer questions.

I would like to remind the public observers at this meeting that public attendees may not participate except at the specific request of the Chair.

The first speaker is Dr. Robert Weiss. Is Dr. Weiss here?

(No response.)

DR. LoCICERO: Our second scheduled speaker is Patrick Martin.

MR. MARTIN: Good morning. Thank you for this opportunity to provide comments to the Panel.

I am Patrick Martin. I'm the Director of Clinical Affairs for LipoSonix, Incorporated. LipoSonix is headquartered in Bothell, Washington, and we are a subsidiary of Medicis Pharmaceutical Corporation.

We design and manufacture a focus ultrasound device that is intended for non-invasive body sculpting applications. Our product is currently available in the European Union, and we plan to submit our IDE application shortly to the FDA.

My comments today will address the questions posted on the FDA's website regarding energy delivery devices for dermatology and aesthetic indications and clinical studies related to those devices. Specifically, my comments will address those questions only as applied to energy emitting devices that are intended for non-invasive body sculpting applications.

We respectfully submit to the Panel that clinical studies for cosmetic devices that are intended for non-invasive body sculpting applications should demonstrate the following: first and

foremost, that the use of the device is safe; second, that the mechanism of action is well documented and understood, that is that the exposure of energy has a controlled, demonstrable and reproducible effect on the targeted tissue as intended; and that patients are satisfied with the aesthetic outcomes of the procedure.

Our first point is that it is paramount that the use of such energy emitting devices must be shown to be safe with minimal risk to the patient and the user. For non-invasive body sculpting procedures, safety can be demonstrated in clinical trials by monitoring adverse events and serious adverse events and the use of standard clinical markers such as blood tests and physical evaluations.

Our second point is that the mechanism of action must be well understood and scientifically proven. In other words, it is not enough to simply claim that a treatment does something and this something results in the end result. Rather, it is important to do the basic science to prove the mechanism of action and how it produces the intended aesthetic result. This can be accomplished in preclinical studies, pilot studies and pivotal studies.

Using our device as an example, it is intended to ablate subcutaneous adipose tissue in a controlled and reproducible manner ultimately resulting in an approved appearance of the patient's abdomen.

To prove this, we obtained histology data from treated tissue harvested from animal and human models. This data showed that the treatment did ablate adipose tissue in a controlled and reproducible manner and that the ablation only occurred in the targeted tissue as intended. Further, we obtained a series of histopathology data over a period of time to show how the resolution of ablated tissue directly resulted in a remodeling of the treated tissue thus producing the desired aesthetic outcome.

So now we can explain directly how the treatment affects the tissue and how the resolution of this effect produces the intended aesthetic outcome.

It is reasonable that other manufacturers should provide such objective evidence of their mechanism of action.

Allow me to add, that this data has been presented at several scientific sessions and it is

publicly available. LipoSonix would be happy to provide this data to the Panel as an example of what can be done in clinical trials and preclinical studies.

The use of pathology histology data has an additional benefit. The lesions that are created in the tissue by our product can be directly observed and measured. This data provides a method to objectively quantify the effect on the tissue.

Our third point is that patient satisfaction is an appropriate primary endpoint for clinical studies related to non-invasive body sculpting. Such patient centered outcomes are the current clinical standard used by plastic surgeons and dermatologists to determine the success or failure of an aesthetic procedure. Experts in aesthetic and cosmetic procedures have submitted written comments to the Panel stating that patient satisfaction is the method to determine success or failure in clinical practice.

If an objective measure of an aesthetic effect is desired for body sculpting applications, it can be provided by secondary endpoints such as changes in waist circumference.

The remainder of my comments will directly

address the FDA's questions presented on their website.

After reviewing the first two questions, we felt they were related and my comments will focus on the second question first.

Regarding the use of patient satisfaction as an endpoint, patient satisfaction is an appropriate primary endpoint. As stated earlier, it is a proper endpoint, the current clinical standard to determine the success of an aesthetic procedure. Allow me to add that a positive patient satisfaction rating should also be accompanied by evidence of an appropriate safety profile and proof that the mechanism of action is well understood and reproducible.

Regarding the question of clinical efficacy or improved health outcomes should be demonstrated or if specific measures of clinical improvement would be appropriate and how large an improvement is necessary, we submit that it is not appropriate to require demonstration of an approved outcome for body sculpting application because as stated yesterday, a vast majority of these procedures are undertaken by patients in generally good health to start with.

Additionally, these procedures are

generally not intended to treat a disease but to provide an aesthetic effect. So there is no clinical reason to expect to see an improvement in health outcome with successful aesthetic procedures.

However, to ensure patient's safety, it would be appropriate that clinical studies for energy emitting devices should show that is no negative effect on the health of the patient.

Regarding the question, should the treatment by such devices be so well understood that the user can preset the amount of change that will occur, we submit that there are currently no standards for the measures to determine the success of a body sculpting application from the American Society of Aesthetic and Plastic Surgery, American Society of Plastic Surgeons or the American Society of Dermatologic Surgery. This is because it is very difficult to create a single metric that will capture all the nuances of body sculpting that can make up a successful procedure.

As stated earlier, the best metric of success in an aesthetic procedure is patient satisfaction, and quantifications of body sculpting outcomes is problematic.

That being said, we do believe that it is

reasonable to expect that the mechanism of action should be so well understood that quantifiable effects upon the treated tissue can be preset and predicted. For example, the use of our device results in the ablation of the targeted subcutaneous adipose tissue. This creates a series of well-defined lesions that are preset in size and location within that tissue. We can measure the effect of change in various treatment parameters that will then affect the change of the characteristics of these lesions. Now this is done through pathology samples of the treated tissue.

It is reasonable for studies related to body sculpting techniques to show such an understanding of this mechanism of action.

For patient safety, it is also important to demonstrate that the preset effects are well controlled and limited only to the intended tissue. Again, this can be demonstrated by evaluation of excised tissue from preclinical pilot studies or pivotal clinical studies.

In summary, we believe that clinical studies for energy emitting devices intended for non-invasive body sculpting applications should demonstrate an appropriate safety profile. It is

also important that the mechanism of action be clearly demonstrated and well understood and this can be demonstrated through the use of human and animal models.

Finally, patient satisfaction is an appropriate primary endpoint for such studies related to body sculpting because this patient centered outcome is the current standard used clinically.

Secondary endpoints may include objective measures obtained from histopathology data or changes in waist circumference measurements. Such an approach would provide a solid basis for scientific understanding of the procedure and be consistent with the current clinical practice.

Thank you for this opportunity to present to the Panel.

DR. LoCICERO: Thank you. I've been informed that Dr. Robert Weiss has arrived. Dr. Weiss, please approach the podium.

DR. WEISS: Thank you. Hello again. Good morning. My name is Robert Weiss. I'm a dermatologic surgeon. I'm in private practice in Hunt Valley. I'm also an Associate Clinical Professor of Dermatology at Johns Hopkins, and I currently serve as the President of the American

Society for Dermatologic Surgery.

I would like to thank this Panel for allowing me to present comments today. I'm representing UltraShape. UltraShape manufactures a focused ultrasound device intended for body contouring and has conducted several preclinical and clinical trials of the device.

I am an investigator in the IDE clinical study that they are currently conducting, and I would like to present our views on suggested safety and effectiveness endpoints for clinical trials for body contouring devices.

My disclosures are that I am an investigator. I'm on the Medical Advisory Board of UltraShape and have been paid in the past small honoraria and travel fees.

I do work with a lot of other companies but those aren't relative and do a lot of research but not relevant disclosure for this morning.

So first of all, what about safety? Potential adverse effects depend on what type of energy source is used, and the effects to targeted tissues must be addressed, locally and systemically. As indicated by the nature of the energy source, the weight is applied and the preclinical data that

demonstrate its capability with respect to the specific target application. Thus careful monitoring of structures in the treatment areas and recording of adverse events should be required as safety endpoints for any type of device and particularly for these types of devices.

For example, the UltraShape device achieves its body contouring purpose by mechanically disrupting and destroying subcutaneous fat cells. The release of fat from these cells and its potential systemic effects are presently being monitored in the study by evaluating clinical chemistry profiles, and these are specifically to assess and examine liver function and blood lipid profiles at various points in time. Other devices that employ thermal mechanisms should be evaluated based on the potential effects of temperature changes on affected structures and then reflected in blood levels.

Reduction in fat thickness is the desired outcome from body contouring treatments and a quantitative objective measure of fat thickness reduction is therefore necessary to assess the effectiveness. And so I would like to go through some of the proposed, some accepted and some rejected, methods of measuring fat.

Obviously we know that subcutaneous fat thickness in the treated area can be assessed using CT images and CT is considered by many to be the gold standard accurately measuring subcutaneous fat thickness, area and volume because of the capability to distinguish between tissue types based on attenuation characteristics. And fat, as we know, has a low attenuation compared to other tissues, rendering the boundary with other structures like muscle, skin and bone readily identifiable.

So as a result, the distance between any two points on an image can be easily and precisely measured.

However, I know and probably many of you on the Panel know that institutional review boards have concerns with the use of CT imaging in healthy clinical trial subjects because of the unnecessary exposure to ionizing radiation. And I certainly would have the same concern for myself. So it seems not to be high on the list for clinical trial purposes.

Ultrasound has also been used to measure subcutaneous fat thickness. The nice thing about ultrasound is that its portable, doesn't emit radiation. We have two units because we do a lot of

venous work in our office that could be used for this. It's less expensive than CT. However, it's very sensitive to the ultrasound technician or whoever is doing the measurements because you have to use very, very light pressure with the ultrasound probe and if you start pressing a little too hard, you're going to affect the thickness of fat that you actually get as a result. So I've seen five different people doing it and get five different baseline measurements. And this has also been borne out in the studies.

So we have found that ultrasound, unless performed by the same person who's expert at doing it at a particular site, can be not that reliable as a measure.

So that brings us to magnetic resonance imaging and why this might be the preferred technique, obviously MRI also has the ability to distinguish clearly and quantify adipose tissue on a very, very precise basis, and I don't need to go through the mechanism of that but I think that the accuracy and precision with which MRI can detect and display adipose tissue has been validated in a number of animal and clinical studies. Animal work in a rat model and human cadavers have demonstrated that this

-- subcutaneous and total adipose tissue volumes calculated from MRI were highly correlated with the extracted, done in a separate section, extracted lipid and fat content determined by dissection.

So basically MRI determination of fat thickness provides an accurate and reproducible measurement of fat thickness reduction and it's safe.

The other things that have been used, calipers, for example, they are quick, non-invasive, inexpensive, theoretically easy to perform, but problems with the caliper technique is that just choosing how much skin to put in between the calipers, choosing the right site, offers a lot of difficulty for inexperienced users and we've also found that these are not reproducible and reliable. And this is even when I trained my own staff to do use the calipers but that's completely dependent on how much pressure, how much fat you pinch. So, you know, it's low cost, and certainly again if you have a single person assigned to do it, it might turn out to be great.

Photographic assessment, at baseline and regular follow-up intervals, does provide visual documentation, and we have found it somewhat useful as long as we have strict procedures in place where

we have footprints on the floor, we have the camera mounted on the ceiling or on a fixed rigid support where the distance between the subject and the camera is identical and the lighting in the room is identical every time, but it can be done, but there needs to be some very good procedures in place.

And then it is also necessary to quantify and account for covariates such as diet, exercise, skin quality, gender, age and BMI. And when designing a body contour device study, it's recommended that the covariates such as diet and exercise during the study be controlled to the degree possible and we encourage our patients not to gain weight and not to lose weight, but it can be difficult and these have to be monitored and kept in the back of one's mind when one is evaluating the data.

So adjusting the covariates may predict the effectiveness and may increase statistical power although I'm not a statistician. So I would leave that to the statisticians.

And then the concerns of the male versus female, a large person versus small person. Obviously if you have a male with a circumference of 45 inches and a female subject with a circumference

of 35 inches, and they both successfully complete the treatment protocol, and let's assume you cover the same area, and you've sliced the same amount of fat, you're going to get a much more profound change in measurements around the targeted area in the small female than you are theoretically in the large male. And so the amount of circumference change might be a lower percentage, with the large male than the small female, but it would still be significant. So that is one of the challenges.

And in terms of investigator global assessments and patient satisfaction assessments, I certainly, we certainly agree that these are recommended secondary endpoints as a means to measure a clinically significant result, with the global investigator assessment using the circumference, weight and appears of treated site or in this case abdomen on day 1 and following a predefined period following treatment, the investigator can assess the results either clinically significant improvement or not clinically significant improvement, and we know that there are a multitude of patient satisfaction or ways to measure patient satisfaction, none presently validated specifically for use in body contour clinical trials, but consistent with trials of other

aesthetic devices, there are definitely definite questions that could be easily asked in a clinical trial and should be required.

DR. LoCICERO: Can you sum up now please?

DR. WEISS: Yes. Sure. Just the issue of the sham control. This has been a difficult factor to incorporate because certainly the person doing the actual physical treatment knows it's a sham treatment and has to be very careful not to discuss this with the subject. The subject is sometimes a little suspicious that they feel absolutely nothing during the sham treatment. So I'm not sure that that's the best control, and let's see. I have one final comment to make.

Okay. Well, in summary there are no definitive data that can be used as a benchmark for effect or ability in designing clinical trials, and it's the responsibility of the manufacturer to design a trial that will support labeling claims, concerning the durability of fat reduction effect. The only thing in the literature are retrospective studies on liposuction which address the issues of long term success but I'm not aware of any device that does that.

And I really thank you for allowing me to

address you this morning, and appreciate your willingness to listen. Thank you.

DR. LoCICERO: Thank you. Is there anyone else in the audience that would like to address the Panel at this time?

(No response.)

DR. LoCICERO: We're open for the Panel to ask questions of the two speakers this morning.

Dr. Newburger.

DR. NEWBURGER: I'd like to ask both Mr. Martin and Dr. Weiss. What is the duration of the studies that you've done? How long after the treatment is completed have you followed patients to see the persistence of results?

MR. MARTIN: We have followed patients to three months and also six months post-treatment.

DR. WEISS: We are planning in this study which is ongoing, planning to do six months from within the study and then like other devices I have, I usually will have patients come back, it might be outside of the study, but I usually will follow them to a year.

DR. NEWBURGER: Uh-huh.

MR. MELKERSON: I'd just like to ask to help the transcriptionist since there are two people

sitting at the microphone, to make sure they identify themselves to help them out. Thanks.

MR. MARTIN: Thank you.

DR. WEISS: Thank you.

DR. LoCICERO: Dr. Walker.

DR. WALKER: It would appear that both of these devices, the targeted tissue is subcutaneous fat, but have there been any other adverse events on other parts of the skin, specifically the epidermal tissue that may end up with either hypo or hyperpigmentation or possibly the dermal effect with the end result of scarring?

DR. LoCICERO: Dr. Weiss.

DR. WEISS: Bob Weiss. I have seen one picture from a patient treated in Spain where they were treated over the iliac crest early in the development of the ultrasound device, and what happened there was there was excessive heat built up. Basically the ultrasound kind of bounces off the periosteum and then back into the skin. So there was a skin breakdown. I didn't see the patient personally, but about a quarter size, and that seemed to heal in subsequent pictures without excessive scarring or excessive disfigurement.

DR. LoCICERO: Mr. Martin.

MR. MARTIN: This is Pat Martin. The current energy levels that are being used in Europe and also that are proposed for our pivotal studies, no, we have not seen any damage to the skin.

DR. LoCICERO: Dr. Newburger.

DR. NEWBURGER: I have two more questions for both of you. Number one, in these studies, are there any biopsies taken at an interval after the treatment to show what the tissue looks like? In other words, the supposed liquid faction of adipose tissue, is that replaced by fibrous tissue? What exactly happens? Do you have that yet?

DR. WEISS: This is Bob Weiss. Certainly we're not planning to do that at our site because this is a patient population that is trying to achieve aesthetic improvement, and it would be very difficult to do a biopsy in that area. I believe the company has data. I know they have short-term data from abdominoplasty just prior to the abdominoplasty where you have some immediate effect results but I'm not sure how much long-term biopsy data there is.

MR. MARTIN: This is Pat Martin. We have done in our pilot studies, studies involving abdominoplasty patients. So patients that were going to have abdominoplasty anyway were enrolled into the

study. There is treatment with our device, and then after a period of residence, tissue is harvested and then we obtained gross pathology and osteology data. We did this anywhere from hours after initial treatment up to 14 weeks after treatment, and what this allowed us to do was not only see the immediate effects of the treatment but also follow the resolution of the creation of lesions and then the resolution of those lesions over time. So we do have data going out to 14 weeks past treatment.

What this has demonstrated to us is that there is a steady infiltration of macrophages which remove the cellular debris and the free lipids and then a remodeling of the tissue and it's replaced by a simple fibrinous tissue.

Also in pilot studies that we've done with patients who are non-abdominoplasty patients, physical exam revealed that there's no change to the physical examination of the patient in the area that was treated. So this area of fibrinous tissue cannot be felt and does not result in any unevenness in the skin.

DR. NEWBURGER: One last question/comment. Both of you are presenting much more detailed protocols to study the mechanism of action and the

safety and efficacy profiles of these devices than I've seen before with similar types of devices, and the 510(k) pathway, unless -- and Mr. Felten could certainly correct me, my understanding is that because of its invocation of least burdensome route, companies can really use the substantial equivalence route and not provide essentially any clinical information. So both of you in essence, am I incorrect, in assuming that you're asking to have the path to come to market become generally more rigorous? Is that correct?

DR. WEISS: This is Bob Weiss. I agree with you. I've been doing device studies for years, and this is certainly the most rigorous study for a device that we've ever done, and that's why I was pleased to be able to testimony in their behalf because I think the bar has been set very high, and I feel very comfortable doing this and we'll actually have real data on a new device which is wonderful to me. I love science, and the more science we can have with these devices, the better.

MR. MARTIN: This is Pat Martin. We agree that these studies need to be very rigorous regardless of the regulatory pathway but I agree with Dr. Weiss, that it is important to have the science

behind this and be able to prove patient safety and a mechanism of action in a very robust way.

DR. LoCICERO: Mr. Melkerson.

MR. MELKERSON: I just wanted to add, through the 510(k) process, when you're looking at different technologies, if they raise different types of questions, in other words, that is where we ask the appropriate amount of information to support an indication and as was described, some of the earlier information on the product, showing that the device actually caused a potential adverse event that we hadn't seen with the other technologies, that also drives us to ask for additional information.

DR. LoCICERO: Dr. Burke.

DR. BURKE: I have two questions. One is how frequent are the treatment for patients and how long do these treatments continue? And then are there long-term follow-ups after the initial treatment? And my second question, I know that Mr. Martin stated that, in fact, that the effect can be preset and predicted, but I wondered how technician sensitive these instruments are. In other words, if one person did one area more than another, would the clinical result be uneven? And this is very important for these devices that have relatively

short training periods and no medical personnel overseeing their use.

MR. MARTIN: With regard to the frequency of use --

DR. LoCICERO: This is Mr. Martin.

MR. MARTIN: I'm sorry. This is Pat Martin. Regarding the frequency of treatment, our device is intended to achieve the aesthetic result in a single treatment. Now, regarding the length of the effect, as I mentioned, we have followed patients up for six months in pilot studies. I don't have data beyond that point at this time.

Regarding the user effect on the patient, I believe both of the products are designed to limit the treatment options for the users. So there's not a great deal of change in the energy output. I can speak authoritative on our device that the user can only adjust the product to levels of energy that we've shown to be safe in preclinical studies.

In terms of a treatment that may have a negative impact upon the patient, in preclinical studies and pilot studies, we have done retreatment of patients and animal models to simulate a user potentially inadvertently retreating an area, and this has shown no ill effects both on the pathology

and histology data as well as long-term follow up studies.

DR. WEISS: Hi. This is Bob Weiss. In terms of the treatment application, it was exactly one of my concerns as well and with this device, with the UltraShape, what they've done is created a computer program using a video camera and positioning dots on the border of treatment so that it's almost like doing a video game. There are dots on the screen and then you slide this hand piece, which the weight of it is the pressure that you use so that you minimize the individual variation and then the dot turns green when it's ready to fire. There's one second cycle times. So you basically look on the screen and follow the dots and then you make sure that you've uniformly applied the energy. That's actually a clever way to do it, and in terms of the number of treatments in our clinical trial, it's three treatments and they're given up to a month apart, and let's see. In the follow up, I think at this point it's going to be three months after the last treatment.

MR. MARTIN: This is Pat Martin. Dr. Burke, I would just add that we see our peak clinical efficacy at approximately 60 to 90 days

post-treatment. With our longer-term six- month studies, we haven't seen any improvement in the outcome or any change in the patient's status.

DR. LoCICERO: Dr. Olding.

DR. OLDING: One of my questions was already asked, but the other one I have really has to do with outcomes, aesthetic outcomes and durability of that outcome. I see so many patients who come in and say, well, I've heard that this does whatever. Would you again discuss how you plan to measure the improvement and how long out you're planning to go. Is it to six months only or is it going to be to a year?

DR. MARTIN: This is Pat Martin. For our proposed clinical study, because we have seen stable results at the three-month mark with no change following patients to six months, our proposal is to have a three-month trial, monitoring the patients to three months. Endpoints we have suggested to the Agency would include for efficacy the use of patient satisfaction as well as waist circumference measurements. We have developed a very rigorous procedure for obtaining reproducible waist circumference measurements, and that seems to show the effects very well.

Patient satisfaction we still believe is an integral part of this assessment because even if they achieve a three or four centimeter reduction in a waist circumference, if it doesn't have the right contour, the right appearance to the patient, it won't be a successful procedure by their standard.

DR. WEISS: This is Bob Weiss. We're using MRI as our most objective measure in calculating volume at a specific anatomic landmark slice. This will be done three months after the last treatment. It seems like with these devices, unlike liposuction, because I do a lot of liposuction as well and have for like the last 15 years, liposuction we get sort of the maximal effects at around, anywhere from 6 to 12 months. With these devices, it seems to be more like three to six months. And then what I find out is as we go out longer, some people say, oh, well, this gives me the license to eat whatever I want, look, I've lost a few inches off my waist and then you have people come back and we've had their baseline weight, and this is after liposuction, they'll come back in here later and say, look, now I've got fat up here. Well, you gained five pounds. So there's sort of the sweet spot where you get the maximal results from the device or from the procedure

that you're doing, and then you don't get into too much of what the patient is doing on their own, and it's been a difficult issue and we've discussed it many times and I think we've chosen the correct endpoints.

MR. MARTIN: This is Pat Martin. If I could just add onto Dr. Weiss' comments. We've established three months as our endpoint. We think it's appropriate because we've seen the stability of the result. We've also seen during the time a very solid safety profile. Looking at our claims for clearance that would be indicated by our clinical trial, and if looking for a claim for a long-term durability, 9, 12, 24 months, we feel that could be addressed by postmarket surveillance to determine the labeling claims for the duration of the treatment.

DR. LoCICERO: Mr. Melkerson.

MR. MELKERSON: I just want to point out that postmarket surveillance in 510(k) generally can only be done under a 522 which is a required study, not necessarily part of a clearance process.

DR. LoCICERO: Dr. Li.

DR. LI: Are there any limits to the length, width and depth of the amount of tissue that you can ablate in this? You know, what are the

limitations or are there any limitations as to who much you can remove?

DR. WEISS: This is Bob Weiss. With the energy setting limitations on the device, I believe it's, you know, each spot is just a few millimeter area and I would have to get clarification of this because this was, and it was several months ago when I looked at that last, and about four centimeters, three to four centimeters below the skin surface, but potentially by changing the design of the transducer in terms of how the membrane that's curved that focuses the ultrasound, obviously you can change the arc, and so you can probably adjust to different depths in the future, but right now it's limited to one depth and defined tissue effect at a certain energy level which are being employed and which were tested in abdominoplasty.

DR. LI: Is there any association with remodeling or any kind of recovery with the amount of material removed? In other words, are there more complications or more adverse effects if you remove a lot of tissue versus you remove a little tissue?

DR. WEISS: I don't have specific knowledge about this device because I haven't tried it at different energy levels, but I know if I translate

from my experience with other devices, typically the more tissue you destroy the more recovery time you have when you're looking at any laser or light source and you kind of trade off. You know, the more downtime, the better the effect, less effect and these are certainly devices designed to walk in, walk out procedures. So I think the concept is to keep the damage minimal.

DR. LI: As I understand it, you have some options in setting the energy that's applied. Is that true or does it just come with the one energy that you use?

DR. WEISS: There's like a low, medium, high setting.

DR. LI: Okay. So I guess my question is would you think there is any relationship between the effect on the patient or remodeling of tissue based on the extremes of the setting? One extreme would be low setting of a short duration and the other end would be high energy, long duration. And then if you superimpose upon that a little loss of tissue versus a large loss of tissue, I mean these seem to be things that a surgeon could, you know, alter if they had a mind to, and if these aren't controlled in some kind of clinical study, it seems like there's a

potential for a vast differentiation of results.

DR. WEISS: This is Bob Weiss. Again with the experience we have with devices, typically what we do is we start off with the lowest settings and then if we're not seeing a clinical effect, let's say it's a multi-treatment trial, then we'll go up in the setting or if the patient is reporting to us like, oh, wow, that really hurts. Well, then we're going to turn that down, and it's more again trying to -- safety is usually the number one issue but under the hypothetical circumstances that you talk about, if it's not limited and someone could theoretically dial it way up, and that person was not trained on using the device, obviously when you're dealing with any energy source, you could get into trouble but I think there are enough safeguards in this device.

DR. LI: Just one last clarification question. Do you have any information about whether or not the extreme settings cause different cellular responses?

DR. WEISS: I personally don't have enough data at hand to answer that question precisely.

MR. MARTIN: This is Pat Martin, Dr. Li. Just to respond to the questions, if I remember them correctly, regarding the energy levels, it is

certainly possible with focused ultrasound to do a tremendous amount of damage or very little damage dependent upon the amount of energy introduced into the body. That's why we spent quite a long time doing bench tests and preclinical studies before going into human tests to make sure that we knew the parameters to insure that we're creating the amount of damage to the tissue in an effective way. So we've established safety parameters that the machine will operate beyond, and it's not possible for the user to adjust that beyond those settings.

In terms of more complications or not related to, I think it was the energy level used, we have not seen that in our trials. Using the energy levels that are in the product currently and that are intended for the pivotal study, in the use that we've been monitoring in Europe, we haven't seen that either. So we feel confident that the levels we have in there do represent a safe amount.

In terms of the remodeling, again we chose the energy levels in the machine to reflect the optimal remodeling effects on the tissue. Now, it is certainly possible someone could design a machine with greater energy levels or less energy levels, to do different sources of creations of those lesions.

For example, the InSitech device uses much higher energy levels for the ablation of tumors but we're not approaching those energy levels.

DR. LI: So just again to clarify, when you say there's no evidence of difference in treatment, but different levels, but I understand that difficulties in doing histology but there's no examination of histology in those cases?

DR. MARTIN: Yes. Yes, sir. I'm sorry. We have different energy levels in the device which can be adjusted to address, as Dr. Weiss, said the perceived sensation of the patient to the treatment as well as to adjust the time of treatment but within that range that's in the device, the lesions that are created have the same appearance and pathology and histology where we've done the abdominoplasties.

DR. LI: Thank you.

DR. LoCICERO: Dr. Anderson.

DR. ANDERSON: Yes, I have a couple of questions. What is the discomfort the patients report from these procedures?

DR. MARTIN: This is Pat Martin. It's very subjective. Some patients have literally slept right through an entire procedure. Other patients have reported pain or discomfort. I don't have a

breakdown of the exact numbers but we have noticed it is tied to the patient anxiety. Patients that come back for a second treatment generally report that it's much better the second time around because of the lack of nervousness. This is a brand new procedure to the marketplace. So they really don't have any sort of metric to gauge it by but patients during the clinical trials have reported to us that, one patient said, you know, this is much less than laser hair removal. But it's very --

DR. ANDERSON: So it's subjective.

MR. MARTIN: Yes, ma'am.

DR. WEISS: This is Bob Weiss. I completely agree. Many patients feel almost nothing and the worst I've seen was like, I feel it a little, yeah, it's like about or just a little bit less than laser hair removal.

DR. ANDERSON: Do they wear a compression garment afterwards like with liposuction?

MR. MARTIN: No, that's not required for our procedure.

DR. ANDERSON: Okay.

DR. WEISS: No, no.

DR. ANDERSON: And then I had another question, after they finished your three treatments

or your one treatment, and I suppose that would be the end of that treatment protocol, if they decide six months down the road or a year down the road they want to do it again, have you looked at that? Is it safe to have subsequent treatments?

MR. MARTIN: This is Pat Martin. We have done safety studies for retreatment at one month post-treatment and two months post-treatment. We haven't done retreatment past that timeframe. But those retreatments have shown that it is safe, both on patient outcomes and the pathology and histology data.

DR. WEISS: This is Bob Weiss. With the study design, we're doing multiple treatments. We do have some experience with that, and I know it's been on the European market long enough that there have been patients who have received treatments like six months later, and there does not seem to be any issues.

DR. ANDERSON: And then just one last thing. What are you proposing as a measure of patient satisfaction?

MR. MARTIN: This is Pat Martin. We have developed some patient satisfaction questionnaires and recognizing these are non-validated instruments,

but we have looked at some of the validated instruments for patient assessment, and we and our medical advisors didn't feel that these were necessarily appropriate and would get us the right information because they're not optimized for body contouring.

DR. WEISS: This is Bob Weiss. I'm trying to remember the study form because we do a lot of studies, whether it's a visual analog scale, and I don't want to give you misinformation. I would have to get back from the study protocol to you.

DR. LoCICERO: Dr. Burke.

DR. BURKE: I have just one follow-up question based partly on what Dr. Li asked and what Dr. Walker asked. Do you ever remove so much adipose tissue that there's skin laxity? And, does that affect the patient's satisfaction?

DR. WEISS: This is Bob Weiss. No, there's not that degree of fat removal.

MR. MARTIN: This is Pat Martin. The same. We don't remove that much adipose tissue. This is not a bulk reduction procedure, and if I could just back up to one point, we were talking about retreatments. For the retreatments, there does need to be an adequate amount of adipose tissue in place

and we do have very strict criteria spelled out in our labeling in Europe for the appropriate thickness before treatment should be undertaken.

DR. WALKER: I have another question. I understand that you're targeting the abdomen here but would there be any limitation to doing additional sites at the same treatment session? Is there any limitation in terms of the outcome or the amount of energy that's being delivered if more than one site was treated at any given session?

DR. WEISS: This is Bob Weiss. The limitation is the energy of the person providing the treatment --

DR. WALKER: I see.

DR. WEISS: -- because it takes a while to do.

DR. WALKER: So the length of time of the treatment is the limitation.

DR. WEISS: Yeah, because you could theoretically mark off another area on the thigh and do it but you're talking about someone being there several hours and --

DR. WALKER: Oh, I see. Okay.

DR. LoCICERO: Mr. Halpin.

MR. HALPIN: Just to clarify for me from a

regulatory point of view, are the products that you're discussing cleared for any other indications or would the clinical testing be part of the package that you would put in the 510(k) request?

MR. MARTIN: This is Pat Martin. Support for the labeling would be provided by the outcomes from the clinical studies. So in Europe, our product is marketed for treatment of anterior adipose tissue.

DR. WEISS: This is Bob Weiss. I think also it would be limited to what was in the study.

DR. LoCICERO: Dr. McGrath.

DR. McGRATH: Just one quick question. How long is the treatment for just the abdomen, just to give us an idea?

MR. MARTIN: This is Pat Martin. With the LipoSonix device, during clinical trials, a single treatment session lasted approximately 35 minutes, 35 to 40 minutes on average.

DR. WEISS: This is Bob Weiss. Similar with the UltraShape, that timeframe.

DR. LoCICERO: Dr. McGrath.

DR. McGRATH: I want to go back to your responses following Dr. Li's question before just to understand these devices better. And I guess this is directed at Mr. Martin since you're the ones that

have done histology, but if you have different levels of energy with different settings that you're applying, I'm surprised that you commented that when you looked at the histology, it was the same. I think I'd like to understand why there isn't a dose response curve on this. In other words, how is the ultrasound exerting its effect, and if you turn up the energy, why doesn't it exert more effect that's perceptible?

MR. MARTIN: My apologies for not being clear. I wasn't trying to imply there is no dose curve effect. Simply that the range that is available in the machine is a very narrow range of energy that we allow the user to select from. So within that range, the tissue damage is substantially equivalent. So we do see that the destruction of the -- is adipose tissue, changes to the collagen and the general appearance.

We have seen in preclinical studies a definite dose curve effect, but we wanted to take up the variability in the system. And so the ability to change the energy levels in our machine are primarily to address the issues related to the patient sensation. So it's not intended to allow someone to create a 1 millimeter lesion and then a 20 millimeter

lesion in actual depth. It's intended to create the same lesion size to get the same effect. However, the fractionated dose we deliver does have an effect on the patient's sensation of that treatment.

So again, the range is relatively narrow. So it does produce relatively the same effect and the same size lesion within the tissue.

DR. BURKE: But the dose delivered is not identical?

MR. MARTIN: No, no, it's not. But this is getting into some of our proprietary design, but the dose range is relatively narrow and it's -- to affect the patient's sensation.

DR. BURKE: And, Dr. Weiss, you don't have any histology. So you don't know what the two different energy levels, what the effect is?

DR. WEISS: This is Bob Weiss. No, the company may have but we haven't done any at our site.

DR. LoCICERO: Dr. Olding.

DR. OLDING: One more question for Mr. Martin. Histologically speaking, does the tissue return to normal? And if it does, when does it and if it doesn't, how long have you followed the tissue out for histologically?

MR. MARTIN: AS I mentioned, we've done the

abdominoplasty on patients up to 14 weeks past treatment, and we have seen at that time, our dermatopathologist has estimated that 95 percent of the lesions are resorbed by that time. Now, we don't have any histology data past that point. We have non-abdominoplasty patients that we've followed up three months and six months and we see an optimal effect at the three-month mark post-treatment.

DR. OLDING: But histologically, I would think there would still be some residual changes if nothing other than scar tissue?

MR. MARTIN: That's correct. Once we kill the fat tissue, it does indeed stay dead, and it is remodeled and replaced by fibrinous tissue.

DR. LoCICERO: Okay.

DR. WEISS: If I could just make one brief comment. This is Bob Weiss. Fibrosis is actually a desired endpoint certainly in liposuction to cause retraction and contraction and releasing the cellular boundaries of the -- sites creating probably a little inflammatory reaction and some fibrosis is actually desired and probably one of the mechanisms of how this works.

MR. MARTIN: This is Pat Martin just to follow up on that. As I mentioned before, the

physical examinations of the patients at three months and beyond, we haven't seen any disfigurement of the skin or it's not possible to palpate this fibrinous layer.

DR. LoCICERO: I have a question concerning the energy transfer. What are the units of measure of your energy? Can you measure the total amount of energy delivered? Can you measure that per unit, a linear unit, area unit, depth, et cetera? What information can that device provide to the user?

MR. MARTIN: This is Pat Martin. The LipoSonix device displays the energy output in terms of the joules per centimeter squared.

DR. WEISS: This is Bob Weiss. Same with the UltraShape device and I'm hoping to be able to examine the MRIs and to see what effect we see, but I think the company can provide very good data. Both companies can provide very good data exactly of the depth and the amount of disruption of fat that occurs and that's why you have to be so tedious of going over that because you're creating such small areas of damage that you have to -- the main thing is to make sure that you apply it uniformly.

DR. LoCICERO: Dr. Burke.

DR. BURKE: I think that I read in the

European literature that there have been occasions of fat emboli after certain devices, and so I don't know if those devices are in comparison with yours but is there any way you can -- how do you check for that or by following the histology, you know, that that's not a potential complication?

DR. WEISS: This is Bob Weiss. I think most of the data with the fat emboli and pretty serious side effects are with the ultrasonic devices that emit the ultrasound from the tip of a liposuction type device, and you can see where you could flip off large chunks of fat doing that, and if people develop seroma as in there's a huge amount of complications but I'm not aware with these devices that there has been anything like that because I probably would have been very hesitant to be a participant in the study if that were a risk.

MR. MARTIN: This is Pat Martin. We've not seen that in our clinical trials, our experience in Europe, nor have we seen reports of that in the literature. I believe Dr. Weiss is correct in that the reports of fat -- or fat -- syndrome have been associated with the externally applied ultrasound assisted devices or the internally assisted devices but given the mechanism of action with the resolution

of these lesions, it is exceedingly unlikely that enough free lipids would be introduced into the bloodstream and appear at a time to cause that risk.

DR. LoCICERO: Dr. Anderson.

DR. ANDERSON: The level of training of the operator, as I understand it from reading in the packet, it might be aestheticians and not necessarily nurses. Is that correct?

DR. WEISS: This is Bob Weiss. I'll answer that we think this is an energy device that probably falls under our Maryland State Regulations that only a PA or nurse practitioner could do and that's who we plan to deliver the treatments in our office to comply with state regulations, but I know those vary state by state.

DR. ANDERSON: Okay. The manufacturer then will have adequate training for other states where the regulations maybe different. Is that --

DR. WEISS: It certainly would be in their great interest to provide that and I imagine they will.

MR. MARTIN: This is Pat Martin. That's correct.

DR. LoCICERO: Dr. Walker.

DR. WALKER: On that same line of thought,

does the equipment itself have some type of safety controls built in to somewhat circumvent the user, perhaps trying to push the machine to operate in a faster mode, just for the sake of time?

DR. WEISS: This is Bob Weiss. There are limitations on total energy, the frequency of pulsing and it's very strictly -- will not actually let you fire unless you're in the correct position as determined by that visual map but then it's calculated.

DR. WALKER: So once that's in place, it can't be overridden by the user?

DR. WEISS: Right. You cannot override that, and there are also internal mechanisms I know that if there's internal calibration, if there's too much ultrasound, it will not fire.

DR. WALKER: I see.

MR. MARTIN: This is Pat Martin. Our device has the same safety mechanisms, and I'm not sure of the exact ones, the UltraShape device, but it is impossible for the user to override the fastest setting in the device. There are also numerous monitoring functions within the device which if it detects improper use, either improper contact with the patient or too much pressure or too little

pressure applied to the treatment and to the patient, the system will warn the user and stop the treatment and instruct them to correct that. Then there's also monitoring of imagery levels as well as for the presence of any abnormal performance of the system along the way. If any energy spike or decrease energy level is detected by the machine, it alerts the user and stops the treatment.

DR. WALKER: So if the machine is being used obviously to work on adipose tissue, does there have to be a sufficient amount there for the machine? Can it calibrate that to fire? So, in other words, if you're someone who is relatively thin or you're over a bony structure, is there some way for the machine to make that calibration or is that the user who's making that determination?

MR. MARTIN: This is Pat Martin. It is the user making the determination of the appropriate area. We provide a great deal of instruction in our labeling as well as instruction with the user during the installment training.

DR. WEISS: Yeah, this is Bob Weiss. I think training is key and it has been emphasized to us, to our site over and over again. You do not treat over bone because the device won't even --

against it. So, you know, all the areas are strictly outlined prior to the treatment and carefully mapped and marked, and it won't allow you treat, one that is marked, it will not allow you to treat outside that area.

DR. WALKER: Okay.

DR. LoCICERO: Dr. Li.

DR. LI: This might be a slightly unfair question but I'll ask it anyway. Do you have any evidence that if you use this, you know, your indication is I guess in the anterior adipose tissue, do you have any evidence that if you use on some other tissue, you get some result you'd rather not see?

DR. WEISS: This is Bob Weiss. Simple answer, no.

DR. LI: So are you aware if it's -- I guess I have a healthy respect for the creativity of dermatologists. Do you have any --

DR. WEISS: Thank you.

DR. LI: Do you have any information about use, you know, use in other fatty tissues besides the anterior for instance? Because I can't imagine that once this is out, that it, you know, people wouldn't sneak into some other area. It would be amazing if

it didn't happen.

DR. WEISS: This is Bob Weiss. I believe the company has -- well, I know the company has imagines of lateral thigh, like saddlebags, done outside of the U.S. and I think, you know, with careful mapping and all the limitations that we were discussing, that it can be safely applied to other areas of fat within an experienced user, but I'll leave the company to address that further, but I'm just not --

DR. LI: I wasn't really -- I guess I was not really aiming so much as the effectiveness in some other area, but was there any evidence for different mechanisms of action in another area?

DR. WEISS: Not different mechanisms. I'm not aware of any.

MR. MARTIN: This is Pat Martin. We have only done histology in abdominoplasty flaps. So it's only the anterior abdomen. However, talking to our dermatopathologist and other medical advisers, there's no reason for us to believe that the mechanism would actually be different in other areas of subcutaneous fat. Again, we're assuming we're treating only the subcutaneous adipose tissue.

In our preclinical studies, we have done

work to examine if there's any ill effect to the treatment if inadvertently treatment has occurred over, directly into the bone or into muscle, and because the entry levels are sufficient to cause a limited amount of damage, you can see damage in the tissue but again, there are safety mechanisms within the machine that give us some feedback on the reflectivity which will trigger a cutoff, that if you're treating over a structure which gets too much reflectivity, that's outside the safety areas.

That being said, we rely a great deal on the training and the education to make sure the user is able to avoid that situation. We try to be very straightforward with customers that this is the effect in subcutaneous adipose tissue, and that's where you should be treating. We try to emphasize that a great deal.

DR. LoCICERO: One last question from Dr. Newburger.

DR. NEWBURGER: I believe that these will be used to treat double chins, and I think that because of the rather intricate anatomy in that area, that there will be issues that one will have to deal with. So hopefully your labeling and your teaching will cover that to avoid those inevitable

consequences.

DR. WEISS: This is Bob Weiss. I agree, wherever there's a way to misuse a device, someone will try to figure out and it's up to the engineers to make sure that that can't happen. With this, with having contact sensors, it's a pretty big delivery thing. It would be very hard right now in its present form to try to treat chins, but obviously people will try that and we will make sure that they don't do it at least on U.S. soil.

MR. MARTIN: This is Pat Martin. Our treatment head is too large to be used effectively on anything but what we call the wide open spaces of the body. We do understand that there is interest in treatment of those areas, but those will require a hardware change to make it accessible.

DR. LoCICERO: Thank you, gentlemen. I appreciate your time.

MR. MARTIN: Thank you.

DR. WEISS: Thank you.

DR. LoCICERO: All of the information provided will allow us to focus very carefully and quickly on all the questions from the FDA.

At this point, Dr. Lim has another announcement to make.

DR. LIM: I mentioned earlier that our press contact for this meeting is Siobhan DeLancey. I believe she is here now, and she's standing. There we go.

DR. LoCICERO: Thank you. We'll now hear the FDA presentation. At the conclusion of the presentation, there will be questions from the Panel.

At this time, our FDA speaker is Mr. Richard Felten.

MR. FELTEN: Good morning. My name is Richard Felten. I'm a senior reviewer in the General Surgical Devices branch of the Office of Device Evaluation, and I guess I'm not conflicted, but I have been involved in the review of most, if not all, the devices that will be on these lists that I will be presenting.

What I want to try to do briefly is give you sort of a brief background history of the devices that are presently cleared for indications for use in dermatology, and how those devices got to market which may actually address some of the questions that came up during the open session.

We're going to briefly show or list the devices that are under discussion here but I want to make clear that our attempt here is not to discuss

specific devices. Our interest is to get feedback from the Panel on the general indications for use area that we are not becoming to see as the use of devices, of all types that had expanded into the dermatology aesthetic "cosmetic" area. And also to provide some background on how we have been evaluating these devices and what the issues are that we are beginning to face with the newer devices. And then, of course, at the end we have some Panel questions.

This is a larger list of all possible energy producing devices that we will probably be asked to review for the expanding dermatology indications for use. And as I mentioned earlier, we're not going to focus or discuss any individual device here, but we just want you to be aware that this is the larger list of devices we are now seeing. Originally it was basically light-based, lasers, LEDs. Today, it's everything on this list and what makes it even more complex for us is in many cases we are seeing these combined so that you may have, for example, a mechanical massager with a vacuum attached, with a RF source, with a LED source, with a laser, all combined into one package for a variety of claims in this new area that we are now dealing with.

Historically, the light-based products were lasers. They were preamendment. They were on the market prior to 1976 for general claims of incision, excision, vaporization, coagulation. Radiofrequency devices also were on the market prior to 1976 for the same or general claims in dermatology. Cryosurgical devices were also on the market prior to 1976 with specific claims in dermatology, but these are the devices that the Center was originally looking at when the Medical Device Amendment was passed.

The larger list of indications we now have on this slide are the things we have now most actively seen. The only one on this list that is unique is the last one with is temporary reduction in the appearance of cellulite. This is a preamendment claim for mechanical massagers and therefore it was grandfathered in. All the other claims on this list are claims that have been added to the larger list of indications after 1976.

And how do we get them there? Well, all of these devices are reviewed under the 510(k) premarket notification system up until today. All the initial clearances though are limited to prescription use device. Today we are now beginning to see some of these devices moving into the over-the-counter area

such as some over-the-counter devices we've presently cleared for hair removal. There is an over-the-counter device now cleared for treatment of wrinkles. What is of importance to remember and is one of the things that came up during your discussion is that all of these indications for use that were on the previous slide were granted to companies based on clinical trial data.

Anytime we see a new technology and/or a new indication for use for an old technology, we have required some type of clinical trial data. Now, the type of clinical trial data may vary depending on the device and the claim but the spread of clinical trial data can go from very simple, make sure you can show it works, to randomized placebo controlled trials which we've been asking for some of the low level laser devices now for pain relief. So we do ask for some pretty rigorous studies under some conditions depending on the device and the indication for use being asked for.

Once we've established that database though then, it does become a technological comparison. For example, clinical evaluation for the treatment of wrinkle was a study where the patients were their own controls. We had baseline photographs before and

after. We used the Fitzpatrick wrinkle severity scale, the elastosis damage scale which is a 1 to 9 scale. For the initial wrinkle treatment devices for ablative, we required a change of two on the elastosis scale. The evaluation was done by masked evaluators, who had photographs handed them in a randomized, blinded manner so they didn't know what the before and after were. The photographs were taken at baseline at various times post-treatment out through six months. For the ablative devices, we required the six month data. And for the initial two or three studies, the companies also provided detailed histological information to show that you could actually see the changes in the damage zone for the increased collagen being produced after the fact.

For hair removal, again the patient is their own control. We do hair counts at a well-defined, tattooed area usually at baseline and at subsequent time after treatment. The criteria here for success for hair removal for the initial devices was at least a 30 percent decrease in the number of hairs 3 months after the last treatment. The number of treatments can vary depending on the device, but again we had a very well-established dataset that we used here.

For acne, again in many cases, the patients acted as their own baseline control. Again, we count lesions at baseline and at variable times after treatment. The success is based on the number of lesions that were resolved, resolution of lesions, not simple improvement. We can't define what improvement means. And usually again it's treatment comparison has the baseline improved. In some cases, acne studies have actually had control lesions or in some cases we actually had split face studies where half the face was treated and the other half was not treated. So again though, it's a process where we can actually count something is measurable.

In other types of clearances like for tattoos, for port wine stains, for vascular lesions, you can't really quantify the amount of clearance. It's a hard thing to do, but photographs very clearly can demonstrate to you that a tattoo got lighter, that a port wine stain gets lighter, that a capillary vessel has gone away. So we did have those kinds of databases even though we made those kinds of clearances.

Today we're seeing this new laundry list of claims which are being added or being requested by us. Body contouring which was talked about here by

the public speakers, change in thigh size, abdominal tightening, skin tightening for the neck and arms, eyebrow lift, eyelid tightening, fat melting which is sort of a generic term being used by many companies and lipolysis but here the term lipolysis means not liposuction but the use of a device to melt fat and leave the fat behind as sort of a catch up after you've done maybe liposuction.

Some of these indications have already been granted. Some are still being asked for which we haven't quite figured out how we're going to deal with them. For example, we have granted a change in thigh size. The company did a randomized control study, one thigh was randomized to treatment, one thigh was to control. They developed a way of replacing a measuring tape on the thigh. They had the same person do all the measurements and they demonstrated that the side that was treated had a significantly greater decrease in thigh size than the controlled side.

On the other hand, we've had people look for eyelid tightening. The problem here is that it can't be measured. I don't how you'd measure how tight an eyelid has gotten, and eyebrow lift is a second one of these areas where we've had trouble

trying to make measurements of these. In these cases, we've had discussions with companies about trying to develop their own way of evaluating these systems basically using photographs that they have developed to show what they believe is a certain amount of improvement varying from 0 to 100 percent, train physicians on those photographs, check the reproducibility of the physicians to actually come up with the same answers every time, that they use those photographs as the template to took at the subject photographs before and after treatment.

Fat melting is another one that we're struggling with, and as we mentioned here, we've asked the companies to do blood chemistries to show that when you essentially melt fat, however you were to define that, is either releasing fat from fat cells or altering it, that that fat that's left in the body isn't going to cause some adverse problems down the road. So, yes, you are correct. We seem to be getting a little bit more tighter with our requirements today than we were 20 years ago maybe. But that's one of the reasons we're having this discussion because this is what we're seeing today.

The question is how do you objectively measure these effects? Can you do reproducible

photographs. You know, all you've got to do is raise your eyebrow a little bit and you've got eyebrow lift. You can smile and make your wrinkles look better. Can you make validated scales that nobody's ever looked at before? How do you do this kind of validation. And then what happens when you have repeat treatments which in many of these cases we're going to see. You know, again when do you look at the outcome, when do you look at the follow up.

Who should be doing the evaluations? You know, should this be physician driven evaluations? Should the investigator be making the evaluation himself? Should you have blinded evaluators who come in and look at people after they've been treated? Or should you be looking at patients satisfaction even though if you're looking at things like body contouring or your eyebrow looks better, your eyelids look tighter, or your smile is better, is it the patient who is the important person here or should we be trying to get the companies to develop some kind of measure tools which have all kinds of built in hazards in many cases.

And I thank you for listening to me. If there's any questions, I'll be glad to answer them.

DR. LoCICERO: Thank you, Mr. Felten. Any

questions from the Panel? Dr. Newburger.

DR. NEWBURGER: Mr. Felten, in the studies which did provide data because they were the first of -- to get that indication, generally how many subjects were in the studies?

MR. FELTEN: If the study is like a randomized placebo control study for like the pain relief studies for low level lasers, they've been averaging in the neighborhood of 125 to 130 patients. They have to have a statistically valid sample size. In fact, I've just been looking at some of our acne studies because we have lots of companies coming in now trying to get over-the-counter acne claims. Those studies have as many as 50 to 75 patients and/or they will be looking at multiple lesions in a patient. They may have 2 to 300 lesions in 25, 30 or 40 patients. So it'll vary.

Twenty years ago when we had basically lasers that simply cut tissue and we just wanted to make sure they were safe and effective for cutting, they might have only had twenty-five or thirty but we probably have required companies to do anywhere from forty-five patients up, depending on what the product is, what the indication for the use is and what the hazard level of that product would be.

DR. NEWBURGER: And also, what percentage of devices that come on the market in this general -- are the -- 2s and what percentage have to -- I've seen that 98 percent are the "me too"s (ph.) that don't have to provide data and don't.

MR. FELTEN: I don't really have the numbers. It's a hard number to look at. I would say from my own experience today, most of what we are seeing are not "me too"s. I think that is what we are struggling with is that most of what we're seeing today are new devices, new technologies and these new claims and almost all of those are being asked to provide clinical trial data. So the more recent clearances I'm suspecting is probably more towards clinical trial data. Ten, fifteen years ago, I would say the majority were the "me too"s, but I don't have the absolute numbers.

DR. NEWBURGER: May I specifically ask you in the area of fractionated lasers, at this point, there are close to 70 of them that are being marketed. How many of the fractionated lasers would you think have provided meaningful clinical data to you?

MR. FELTEN: They all have been asked to do clinical data and if they got a clearance, they would

have had clinical data that we would have accepted. All the fractional lasers are being treated as new technology. They are not being "me too"ed to the previously marketed lasers. The initial ones have all provided histology to show depth and penetration, zones of thermal damage, zones of coagulation, and then as they've added claims for wrinkles or melasma or something, they've all had to provide clinical trial data at the same level that we used in the previous clearances.

DR. NEWBURGER: Thank you.

DR. LoCICERO: Dr. McGrath.

DR. McGRATH: Two questions. With regard to photography, I mean you're raising the point that photographs are difficult to evaluate but there are systems and I think we mentioned this briefly yesterday that some of our scientific journals and our examination processes are now requiring the physician to use a photographic storage system that has an authentication mark in the corner, that the photo has not been in any way Photoshopped. And have you ever considered that putting something like this into place might be useful for the purposes of having a higher level of confidence in the photography that's done for the purposes of this kind of a

evaluation, I guess I would ask number one. And, number two, I wanted to ask you about the blood chemistries and the sensitivities of these for the amounts of things that you might be seeing in a situation with fat melting or whatever, because I think as practitioners, the thing we're always asking for again is what is the fate of these materials, and can you detect any of those in the bloodstream? Are you seeing anything? Is that really what we really need or do we need blocks of local tissue or needle biopsies or something of that sort to really let us see what's happening at the site as well as the breakdown of the products that are chemically present at that point.

MR. FELTEN: First of all, regarding the photographs, no, we haven't done made the requirement. Interestingly enough though, I have just attended a meeting back this summer where somebody pointed out that even if you establish that kind of a criteria, that it has been Photo Shopped, you can actually alter the quality of the photograph simply by altering the lighting of the photographic system itself. By shadowing or removing shadows, you can have reproducible photographs but by changing the lighting, you actually can change what you can see in

the photograph to remove I guess or add whatever you want to have there. So reproducible photographing can be done but even the quality of the lighting, even if you've got the same lighting time after time after time, if you just change it slightly, you can make things look better.

I can't really answer the one about the blood chemistries. We're asking for that. I really can't address what's going on with those because the studies are ongoing now. So it's all proprietary information.

Again, many of these new technologies like that though, we are asking for the histology because we ourselves would like to see, you know, can you reproduce what you claim you're doing and show us the histology so we can see what his happening in the adipose tissue and so on. But we are asking for the chemistries and we haven't yet I guess reached the conclusion whether they are or are not giving us what we want.

DR. LoCICERO: Okay. Dr. Newburger.

DR. NEWBURGER: Your point about alteration of photographs is very well taken. I had just earmarked my favorite photo here of the patient before and after and before the patient is on a chin

rest and it's like this, and then after the patient's on the chin rest like this and, you know, there certainly is a difference.

DR. LoCICERO: For the transcriber, the first, before is hard against the hand and the after is the hand is near the chin. Other comments, questions?

(No response.)

DR. LoCICERO: Just to, I know that in a presentation earlier during this Panel time, there was discussion of the matrix which is a new innovation for the FDA reaching from division to division for information. Has that extended or is there any thought of extending this to reaching across departments to look for additional resources and I'm speaking specifically here about what Dr. McGrath was talking about in terms of photography. There are other divisions within the Government that have excellent photographic analysis software and hardware, and would it be possible for the FDA to reach across departments to access those sorts of resources?

MR. MELKERSON: Currently the FDA matrix is limited to CDRH. But in terms of outreach, one of the missions of that group is how do we leverage

outside resources. So the short answer is we haven't yet. The internal matrix is just now internal to CDRH.

DR. LoCICERO: Thank you, Mr. Felten. We appreciate your time.

We are running slightly ahead of schedule. I think it would be good to take our break at this point. We'll reconvene at 10:00 sharp.

(Off the record.)

(On the record.)

DR. LoCICERO: So we would like to get our Panel reconvened, so that we can conclude the business of today.

We've had our public speakers. We've had questions to the public speakers. We've had our FDA presentation and questions to the FDA concerning that presentation, and we're going to shortly being to address the questions that the FDA has for us on these clinical trials.

So I'd like to begin by asking our Panel members for any general comments and thoughts before we look at the questions from the FDA.

We're going to begin this time with our surgeons and work the other direction. So we're going to ask both Dr. McGrath and Dr. Olding to make

their general comments now. Dr. McGrath.

DR. McGRATH: Can I defer my comments until a little later?

DR. LoCICERO: Dr. Olding.

DR. OLDING: Obviously a safety profile is paramount here, but so is patient satisfaction. And I believe that hopefully the discussions today will be a little bit easier than the ones yesterday. But I believe that it's going to be difficult again to look at all of the parameters of evaluation for and make general suggestions rather than take each one individually.

DR. LoCICERO: Dr. Newburger.

DR. NEWBURGER: I'm certainly encouraged by the rigor with which safety issues are being looked at. My general comment about safety is I'm hoping that the effects of these devices will be looked at over a longer period of time before they're actually cleared because we've seen with many other devices that adverse events may start to show up 7, 8 or 10 months post-treatment. I won't mention the particular devices where that occurred, but it was very significant.

So depending what class of devices we're looking at, I do hope that the duration of looking at

the safety profile will be extended beyond six months.

DR. LoCICERO: Dr. Burke.

DR. BURKE: Well, it was very interesting hearing the presentations today when the devices are being very carefully looked at, and I especially like seeing histology so that we can understand as much as possible how these instruments work. I think we have to be cautious about the other instruments that are, other devices that are theoretically ME2s but may have different implications and I think that we have to know that the instruments themselves have settings as mentioned this morning that kind of assures safety because I think that the use of these devices by non-medical personnel implies that, and I, in my own practice, have seen side effects from misuse of devices. So I think that's the thing that we have to be very cautious in assuring that the devices, that they are safe when used by personnel that may not understand all of the possible implications or misuse or overuse.

DR. LoCICERO: Dr. Walker.

DR. WALKER: You know, I, too, am encouraged by the emphasis on the safety of these devices which I think is paramount and also education

of the end user which probably in many of these situations, not be a physician. So there's some additional precautions that should be set in place by the sponsors to make sure that there's enough education and supervision in place for some of these devices. Although they're low energy, they still potentially have the ability to damage tissue beyond the targeted site.

In addition, I also am very encouraged by the emphasis on the science of these devices and the FDA's basically demanding that it's proven that they work. I think that's important, and lastly, the concern about evaluation of endpoints because the market that these devices will be targeted to are primarily aesthetic. I think coming to some consensus on whether or not patient satisfaction is sufficient for evaluation of the end result is also important.

DR. McGRATH: Thank you for letting me put my thoughts together before speaking. Speaking about the new indications that you brought to the podium right before we took our break, I think that a lot of these are very confusing to clinicians, and I want to speak on their behalf. Not only are we seeing these devices and debating whether they would have utility

in our practices, but even if we don't choose to use them, we're being asked continually by our patients about whether they should use these.

So I think it's very important for us to have a clearcut picture in our minds about the effectiveness of some of these new things, and Dr. Walker just alluded to that. I think we need to have endpoints where we have some proof of effectiveness and some sense of how to quantify that for our patients and what they can expect, to what degree, with some of these.

And also I think with these, we have got to ask for very clear information about safety parameters and I'm particularly interested in tissue effects and systemic effects and would feel strongly that this is information that our patients have to have and we have to have before we know how to deal with these new things in practice.

DR. LoCICERO: Dr. Li.

DR. LI: I have perhaps a non-clinical view of this, and first of all, the idea of calling these low energy devices I think is a little misleading because if you're a cell, it's not particularly low energy that we're dealing here because the whole idea is that you're killing cells with these devices.

So in a biological sense, they are certainly high enough energy to do harm if you misuse it intentionally or unintentionally. So I think to think that they're safe because of the term low energy is a mistake.

The other, as I go through the types of energy that were delivered from the FDA standpoint, I'm not sure how we can discuss these as a group because the mechanism of action are completely different. I'm not completely familiar with some of these but just reading down the list, it would appear that some of these call cell death by perhaps directly disrupting the cell wall. Others probably heat up the local water or surrounding tissues somehow to the point where some cell goes apoptosis. One is cryogenic. So the method of that cell death is, you know, some ways completely opposite of the cell ablation, and then there's things like the mechanical massage therapy which I think, unless you've got really strong fingers, probably really doesn't cause any cell death at all.

So we're asked basically I think to somehow evaluate all these devices with at least four different mechanism of action, and then you superimpose upon that with each method, there are

levels or intensities of light or energy that one could use as well as the area and depth to which you can treat, that the number of invariables just seems absolutely enormous, and as much as the cell histology is done, you know, as we've heard, you know, they just simply haven't had the time to actually explore all the histology. And, histology I think if you just, I mean it's a start to take histology immediately after the procedure but these procedures are meant to ablate cells and then cause remodeling. So we have no idea actually what the nature of the remodeling is as a function of all the variables that we just saw. So we're left with these devices that seem kind of like a magic wand, if you wave it over certain areas, you know, you seem to remove tissue, but there seems to be, at least from where I sit, extremely little information over the exact mechanisms of action. So in the absence of that, it seems a little bit, and then superimposed upon that the creativity of dermatologists to use this thing wherever they could possibly wave it over, it's daunting to me to try to come up with one set of conditions or protocols that would recover them all.

DR. LoCICERO: Mr. Halpin.

MR. HALPIN: From an industry point of view

without specific sponsors and specific products, I'll speak generally to what I think the process is from a manufacturer's point of view.

One of the things to point out is although these are 510(k) products, they fall under the regulations which include design control. And part of design control would include risk analysis where you evaluate potential risks of the product, the technology and the way you're using the technology.

In addition, it would also include software/hardware verification and validation activities to make sure that your inputs are actually being met by the performance of the product.

In addition, there's also something called design validation where you actually take the product and use it according to its intended use to demonstrate that it works the way it's supposed to including working according to its labeling.

So I think if you look at the two examples of the products that were under testing that were discussed in the open session this morning, those are good examples where I think they're following design control and then going through the process of actually taking that product to its intended use and actually demonstrating that the product meets the

label requirements and the indications that they'd like to have for that particular product. So I think from an industry point of view, it appears that a lot of the right stuff is in place from a safety and effectiveness point of view.

I wanted to speak to one other thing which is we talked a little bit about photographs and trying to make sure photographs are the photographs that are supposed to be. I think from an IDE clinical trial setting, you run into this with data in general and data integrity, and I think the GCP clinical trial process is probably a good place to actually try to make sure that you're taking care of any dataset including photographs. I think they fall into that, and I think there are control mechanisms you can use in addition to, you know, authenticity or other things in order to say, you know, are you doing things the right way in this clinical trial citing this as data including photographs valid.

DR. LoCICERO: Ms. Rue.

MS. RUE: Well, I concur with most everybody's discussions on safety and efficacy, but I think we just really need to also be concerned of the uses outside the medical arena.

DR. LoCICERO: Dr. Anderson.

DR. ANDERSON: I share some of the concerns about the necessity of adequate training for non-medical personnel who may be using these assessments, and I think that's something that the sponsors will have to address in some manner.

I'm also wondering with these devices if the FDA has some equivalent devices that they may be able to use as a reference point to assist in guiding the sponsors with regard to these different devices.

And finally with regard to endpoints, and I'll speak directly about patient satisfaction, this has been a very difficult issue to address in the plastics arena, and I've tried to address it myself for about 18 years with little success in finding an assessment that is one size fits all. I can tell you why various quality of life and outcome assessments might be inappropriate for testing of some of these devices.

Therefore, I think that we may be forced to rely on sort of a global patient satisfaction assessment with regard to satisfaction until that assessment that is being worked on by ASPS is available.

DR. LoCICERO: Dr. Gooley.

DR. GOOLEY: Well, from a statistical

standpoint, I really don't have any comments although I would like to say that I was quite impressed with Mr. Martin and Dr. Weiss' descriptions of their trials and their rigor and thoughtfulness. I thought they were considering things, safety and efficacy very appropriately but statistically, I don't really have many comments this morning.

DR. LoCICERO: So I must say that I also was quite impressed with the presenters this morning and with the written material that the Panel received beforehand, that uniformly, everyone asked the FDA to do their job which I thought was fascinating because a lot of times we get presentations where there are suggestions for how the FDA can do their job in a different way, so that everyone asked for safety first and proof of effectiveness through science. I thought it was great, and I have to applaud this country I guess as a change in thought process. We actually now are saying the same thing on both sides of the table today. That's great.

So I think at this point, we're ready to focus our discussion on the FDA questions.

Copies of the questions are in the Panel's folder. We're ready.

MR. FELTEN: The first question to the

Panel is what would be acceptable, clinical study endpoints for devices that are not intended to be therapeutic, that is, for devices intended to have indications for use such as a change in the appearance of cellulite, a temporary change in the appearance of cellulite, for body contouring, for body contouring through fat reduction and, of course, those other ones that were on our list, for eye lift, eyebrows and basically all of those indications would fall under this question.

DR. LoCICERO: So soft science. Okay. Comments. Dr. Walker.

DR. WALKER: This is such a subjective area. It would have to be -- it's always going to be the person who's requesting these improvements who's also going to be the same one who's evaluating the effectiveness of that improvement. If there was some way to actually change the appearance of cellulite, I don't think there would be any real discussion whether or not that actually changed. I think that you would get some immediate feedback, positive or negative. For body contouring, the same. Dr. Weiss earlier -- well, I'm sorry. (d) for body contouring through fat reduction, he did allude to the fact that they're using MRIs as to objectively evaluate that

fat reduction but in the real world, that is probably not realistic.

However, for study purposes, that may be a way to find an objective measure at least in that regard.

The other two, it's really hard for me to really comment besides global patient satisfaction.

DR. LoCICERO: Dr. McGrath.

DR. McGRATH: That obviously is key but I think patients are asking and again professionals are asking for more information about, and I'm just going to talk right now about the effectiveness side, I think that clinical study endpoints should include the degree or level of effectiveness of the device. In other words, the power of the intervention. I think there has to be information about duration. People are asking about that. They want to know how long the effect will last. I think there should be information about who, in other words, in terms of patient selection and which patients would be the best, would some be so obese that this would be ineffective in that setting is what I'm getting at. And by starting to amass these pieces of data from clinical study endpoints, I think then we can talk about these more rationally when people ask us about

whether or not they're effective. So I think these are endpoints that we've got to have if we're going to put these there with any certainty that we can comment on whether these things are effective for the person standing in front of you because I think that front end guidance is just as important as the back-end satisfaction later on.

DR. LoCICERO: Dr. Newburger.

DR. NEWBURGER: My understanding about the origins of some of the FDA's mandates were to prevent basically consumer fraud early in the 1900s. And it would certainly seem in the marketplace which has nothing to do with what we do here today in terms of safety and effectiveness, we've seen many devices that basically, you know, are probably safe but they're really doing nothing more long term than a wallet biopsy for the patient.

So I love data, and I love meaningful, reproducible data. We've seen a lot of devices that cause temporary effects basically by virtue of the edema that's generated during the destructive process, and then you see at a period of between three to six months, the effects start to minimize and, you know, maybe you're back at go at the end of a year. So in terms of effectiveness, I really would

like to see, depending on what the modality is, I'd like to see the washout period of these devices being established that will help the clinician given better guidance to their patients and also will help the clinician if they are given these treatments to protect their own reputations.

I think that there must be a way in terms of three-dimensional imaging that one can get a physical way to look at global assessment, and this could involve general decrease in volume, in area. It would also be a mechanism where you could look to make certain that there isn't an irregularity in the contour, for example, when you're using a fat melting device, so that you don't get dimpling or an exacerbation of the appearance of cellulite. And whether it's holographic type of situation or a Vectra type of device, in the greater scheme of things with a study, these are not unaffordable and it would give me more confidence because it is harder to alter those images than it is with some of the Photo Shop programs that are very creative.

So I really would encourage a more global way in addition to global assessment from a subjective point of view and observer's point of view. I think it would be a significant endpoint to

have an objective measurement that really could be reproduced on a three-dimensional basis.

DR. LoCICERO: Dr. Anderson.

DR. ANDERSON: I think as a minimum, we need to be able to tell the patient a few things, and that would be the expected range of results, as well as the patients who are most likely to achieve benefit from a given procedure.

I also think we should be able to tell the patients the estimated, at least, length of the benefit, and then I've already mentioned satisfaction. I think that satisfaction has to be an endpoint.

DR. LoCICERO: So before we make our final comments to FDA, let's have some more discussion about imaging technology. We've talked about photographs and 3-D imaging and MR as potentials. Are there any other technologies we should be considering? Mr. Halpin.

MR. HALPIN: I think the one thing we don't want to rule out is the blinded, live assessment and the patient assessment, not necessarily that those are by themselves adequate, but I think that in some of my past experience, I've seen photographs or other things that don't really truly reproduce what can be

seen by a live evaluators and don't necessarily reflect what the patients are actually feeling when they're doing their self-assessments even in a blinded fashion.

DR. LoCICERO: In terms of that, should the patient serve as their own control as the FDA has used in the past?

MR. HALPIN: I think from an industry perspective, given that there are so many different potential endpoints and affect treatments in the sizes that could be involved in this question, that I would think that you would want to leave that as an option.

DR. LoCICERO: Dr. Burke.

DR. BURKE: With the caveat that the technician pressure is very significant. I think ultrasound is inexpensive and possible and there are ways to have a simultaneous measurement in the instrument of the pressure on the skin. So you could -- I mean this is something that could be very minimally refined to make it reproducible.

DR. LoCICERO: Would you use 3-D ultrasound, 4-D ultrasound?

DR. BURKE: I mean I'm not familiar -- I mean I would have to see the price and the time and

the everything for the various ones but I would use one of those I would say. I'm not familiar with the difference between the 3-D and 4-D ultrasound.

DR. LoCICERO: Anybody want to speak to that?

(No response.)

DR. LoCICERO: So the 3-D is a reconstruction of a slice and the 4-D is something where you can see something over time. That might be something that could be used during treatment to look at change but there may be other technologies as well.

DR. BURKE: Well, then I think if you're using 4-D, you have to have a reasonable time after treatment because of the edema during and just after the treatment.

DR. LoCICERO: It's live simultaneous. 4-D is used mostly for fetal imaging.

DR. BURKE: Uh-huh.

DR. LoCICERO: And watching changes. So that's a little different. Other comments.

DR. OLDING: I would like to make one more general comment. It seems as though the amount of change that we're talking about in these patients is relatively small. We didn't have that presented

today but even in patients that I've done standard liposuction on and suctioned out what sounds like to be consider amounts larger than what we're discussing today, it's sometimes difficult without having that precise photograph, pre and post-op photograph next door to one another to determine exactly where I did the liposuction.

And if we're talking about smaller areas, and smaller changes, I think we have to be very aggressive about looking at those methodologies and making certain, depending upon the device, on the variabilities of what we're talking about, that we're more critical about it than in some other processes that we've discussed in the past.

DR. LoCICERO: Dr. Burke.

DR. BURKE: And this is one other general comment. I think that for these devices, I would recommend having kind of a mandatory labeling that says, with a box head sort of stating absolutely the safety precautions. In other words, don't do this and don't do that, another paragraph stating who are the patients most have to benefit. And third, real time specific definition of temporary. Do they mean the temporary reductions will be days, weeks or months? And I don't think that they should have the

vague term temporary as a label.

DR. LoCICERO: Dr. Li.

DR. LI: I would request that as many quantitative measurements of these changes should be made. For instance, the amount of tissue loss and, you know, where it was taken, because I think in the absence of that quantitative information we'll never really get to some endpoint where if we want to see if there's an effect of the amount of tissue loss, or its location with some adverse effects, it'll just get lost in the qualitative type of data.

DR. LoCICERO: Mr. Melkerson, I think the Panel is pretty clear on this, that safety is an important piece but besides that, in terms of endpoints for contouring, temporary or semi-permanent, that there would be a profile of the changes and that that information can be codified and given to the user and the patient, and that there should be some hard endpoint but the Panel is sort of split.

In addition to appearance and satisfaction, that there must be some imagine evaluation and a variety of images, imaging technologies and techniques were provided as examples.

Does this answer -- does this satisfy the

FDA?

MR. MELKERSON: Actually I had one slight question to make sure I'm clarifying the safety. Yesterday we had talked about issues related to sensation? In other words, we talked about damage, some of these things are damage to a material or, you know, are there sensational issues? In other words, you couldn't palpate the difference but does the patient feel the difference? So issues related to sensation or whatever, should that be included in the safety profiles?

DR. LoCICERO: Dr. Newburger.

DR. NEWBURGER: I think it should be included in the safety profile. I think it would be very helpful in this type of situation to also include patient diaries relating to sensory issues as well as any changes in surface characteristics. Are there burns, hyper and hypopigmentation? I think that that should be part of, on a very precise basis, the safety -- in the safety guidelines.

DR. LoCICERO: Dr. McGrath.

DR. McGRATH: One other thing with these devices that possibly in terms of -- now we're talking about safety that should be thought about is whether it might not be a good idea to expand the

premarket studies to include more than the abdomen. I mean I think we're all agreeing that once these devices are available, certainly people won't hesitate to reach over six inches and put it on the thigh, but it also will go onto areas where a lot of questions start to be raised, and I think it's kind of disingenuous to say, well, we'll get it approved for the center of the abdomen and then kind of wait and later on figure out where people decide to use it and then double back with whatever post approval studies to look at its effect here or there.

So I wonder if we shouldn't think about this prospectively and be aware that perhaps the thighs may behave a lot like the abdominal wall but suppose someone uses it on the super pubic fat or suppose someone uses it on the arm where this proximity to the, you know, the great nerves going down to the hand and wrist or suppose someone does use it as we mentioned earlier this morning on the neck.

And I think also there may be other things that I've heard people mention, colleagues before I came here, that we should probably think about and, for example, one might be what about someone who comes in who's pregnant, and should there be some

thought about whether someone perhaps in the first trimester of pregnancy, are there any issues with doing ultrasound to the super pubic or the mid abdomen and that type of thing that we may not even be brining out today that really need to be thought about more deeply before we agree that ultrasound delivery in various doses is entirely safe to the abdominal wall particularly of young women.

DR. LoCICERO: Does this satisfy the FDA?

MR. MELKERSON: Thank you for the clarification.

MR. FELTEN: The second question, for dermatologic energy delivering devices intended for aesthetic/cosmetic/non-therapeutic improvement that are low risk, is patient satisfaction alone sufficient to support market or should scientifically validated evaluation scales be developed possibly including masked evaluations? Should the treatment also have a clinical efficacy? For example, should body contouring/reduction of abdominal fat also show an improved health outcome? If clinical outcome is necessary, what specific measures of clinical improvement would be appropriate and how large of an improvement is necessary?

DR. LoCICERO: We started to answer some of

this before. Ms. Rue.

MS. RUE: I just wanted to say in listening to this that especially with a focus on childhood obesity that this nation has, I think there needs to be some discussion and addressed on age appropriateness for this procedure also.

DR. LoCICERO: That's an excellent point not brought up before. Thank you. Additional comments? I think we've been addressing the issue that patient satisfaction is important but not the only measure and that there is some potential for using a more scientific endpoint as an additional piece of information. This question asks more detail in terms of a validated evaluation tool and potential for improving health. Again, we're a little bit -- Dr. Anderson, I know you've spent a lot of time in this area. So maybe you have some comments to get us started.

DR. ANDERSON: I was making some notes.

DR. LoCICERO: Maybe Dr. McGrath can.

DR. McGRATH: Well, first of all, there's two questions embedded in here, and I think the first one is should the treatment have a clinical benefit? And I think the answer to that, if you're speaking about clinical as medical, other than psychological,