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UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION

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MEDICAL DEVICES ADVISORY COMMITTEE

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GENERAL AND PLASTIC SURGERY DEVICES PANEL

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GAITHERSBURG, MARYLAND

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THURSDAY,
JULY 24, 2003

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8:50 a.m.

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The Panel met in Salons A, B, & C, Grand Ballroom, at the Gaithersburg Hilton Hotel, 620 Perry Parkway, Gaithersburg, Maryland, with Robert L. McCauley, M.D., Acting Chair, presiding.

PRESENT:

ROBERT L . McCAULEY, M.D., Acting Chair

MICHAEL A. CHOTI, M.D., Voting Member

PRESENT (Continued):

MICHAEL J. MILLER, M.D., Voting Member

BRENT BLUMENSTEIN, Ph.D., Temporary Voting Member

RAYMOND J. LANZAFAME, M.D., Temporary Voting Member

ANN MARILYN LEITCH, M.D., Temporary Voting Member

JOSEPH LoCICERO, M.D., Temporary Voting Member

DEBERA M. BROWN, Industry Representative

LeeLee DOYLE, Ph.D., Consumer Representative

DEAN E. BRENNER, M.D., Consultant

FRANCINE HALBERG, M.D., Consultant

DANIEL B. KOPANS, M.D., Consultant

STEPHEN SOLOMON, M.D., Consultant

CELIA WITTEN, Ph.D., M.D., FDA, Division Director DGRND

DAVID KRAUSE, Ph.D., Executive Secretary, Division of General, Restorative & Neurological Devices/ODE

ALSO PRESENT:

BINITA S. ASHAR, M.D., Division of General, Restorative & Neurological Devices

GEORGE M. BURDITT, Kelsey, Inc.

KAMBIZ DOWLATSHAHI, M.D., Professor of Surgery, Rush Medical College, Kelsey, Inc.

KEYVAN FARAHANI, Ph.D., NIH/NCI

ROBERT GATLING, Office of Device Evaluation, FDA

NEIL R. P. OGDEN, Branch Chief, General Surgery Devices Branch

JUDITH E. O'GRADY, RN, MSN, RAC, Senior Vice President, Regulatory, Quality and Clinical Affairs, Integra LifeSciences Corporation

JOHN D. PAULSON, Ph.D., Vice President Quality Assurance and Regulatory Affairs, Johnson & Johnson Wound Management, a Division of Ethicon, Inc.

LENE RETBØLL MÜLLER, Director of Quality Assurance, Medical Devices, Ferrosan A/S

ALSO PRESENT (Continued):

STEPHEN P. RHODES, MA, Branch Chief, Plastic and Reconstructive Surgery Devices Branch

C O N T E N T S

P-R-O-C-E-E-D-I-N-G-S

(8:38 a.m.)

DR. KRAUSE: Good morning. We are ready to begin this, the 62nd meeting of the General and Plastic Surgery Devices Panel.

My name is David Krause. I'm the Executive Secretary of this panel, and I'm also a reviewer in the Plastic and Reconstructive Surgery Devices Branch.

I'd like to remind everyone that you are requested to sign in on the attendance sheets which are available at the tables just outside the doors. At the table out there you may also pick up an agenda, a panel roster, and information about today's meeting.

The information includes how to find out about future meetings through the Advisory Panel phone line and how to obtain meeting minutes or transcripts.

Before I turn this meeting over to Dr. McCauley, I'm required to read two statements into the record. One is the deputization of temporary voting members, and the second is a conflict of interest statement.

Now, only panel members who are attending this morning portion of the meeting will need to be deputized

because there will be a vote. This afternoon's portion of the meeting will not have a vote. So those members do not need to be deputized.

Pursuant to the authority granted under the Medical Devices Advisory Committee charter, dated October 27th, 1990, and as amended August 18th, 1999, I appoint Brent Blumenstein, Raymond Lanzafame, Ann Leitch, Joseph LoCicero as voting members of the General and Plastic Surgery Devices Panel for this meeting on July 24, 2003.

In addition, I report Robert McCauley to act as Temporary Chair for the duration of this meeting.

For the record, these individuals are special government employees and consultants to this panel or other panels under the Medical Devices Advisory Committee Act. They have undergone the customary conflict of interest review and have reviewed the materials to be considered at this meeting.

And this appointment is signed by Dr. David Feigel, who is the Director of the Center for Devices and Radiological Health.

Okay. The following is the conflict of interest statement.

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety. To determine if any conflict existed, the agency reviewed the submitted agenda for this meeting and all financial interests reported by the committee participants.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interests. The agency has determined, however, that the participation of certain members and consultants the need for whose services outweighs the potential conflict of interest involved is in the best interest of the government.

Therefore, a waiver has been granted for Dr. Michael Choti for his interest in a firm that could be affected by the panel's recommendations. Dr. Choti's waiver involves consulting on a competitor's unrelated product for which he receives an annual fee of less than $10,000. The waiver allows this individual to participate fully in today's deliberations.

A copy of this waiver may be obtained from the

agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

We would like to note for the record that the agency took into consideration other matters regarding Drs. Choti, McCauley, and Solomon. Each of these panelists reported past or current interests involving firms at issue, but in matters that are not related to today's agenda.

The agency has determined, therefore, that they may participate fully in all discussions.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants should excuse him or herself from such involvement, and the exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

Those are the two statements. I'd also like to say that anyone addressing the panel or any panel members when they speak, please speak clearly into the microphones

so that the transcriptionists can fully understand your statements.

And one other thing before I turn the meeting over to Dr. McCauley. I would just like to thank Dr. McCauley for his service to this panel. This is Dr. McCauley's last meeting unless we happen to have another one before August 31st, which would be really hard to schedule at this point. So I told Dr. McCauley that he's free to do any outrageous things he wants because it's his last meeting and we can't fire him.

(Laughter.)

DR. KRAUSE: So anyway, Dr. McCauley, please.

ACTING CHAIRPERSON McCAULEY: Good morning. I'm Robert McCauley, and I'm the Chief of the Department of Plastic and Reconstructive Surgery at Shriners Burns Hospital and Professor of Surgery and Pediatrics at the University of Texas Medical Branch in Galveston.

And as Dr. Krause mentioned, I am currently the Acting Chair for this session.

Today the panel will be making recommendations to the FDA on the proposed reclassification of absorbable hemostatic agent and dressing products from Class III to

Class II and on clinical concerns involving medical devices intended to ablate or remove breast tumors.

The next item of business is to introduce the panel members who are giving of their time to help the FDA in these matters and the FDA staff here at this table.

I'm going to ask each member to introduce himself or herself, state his or her specialty, position, institution, and his or her status on the panel. That includes voting members, industry or consumer representatives, or deputized voting members.

I would like to start with my immediate left.

DR. LANZAFAME: Hi. I'm Raymond Lanzafame. I am a general surgeon. I am currently the Director of Laser Medicine and Surgery at the Rochester General Hospital in Rochester, New York, and I am a deputized voting member of the panel.

DR. LEITCH: I'm Marilyn Leitch. I'm a surgical oncologist in the Department of Surgery at University of Texas Southwestern Medical School in Dallas. I'm the Medical Director for the Center of Breast Care there.

DR. CHOTI: I'm Michael Choti, surgical oncology, general surgery at Johns Hopkins Hospital in

Baltimore, Maryland, and I'm a voting member of the panel.

DR. BLUMENSTEIN: I'm Brent Blumenstein. I'm a biostatistician in private practice, and I'm a temporary voting member.

DR. DOYLE: I'm LeeLee Doyle. I'm the Associate Dean for Continuing Medical Education and Faculty Affairs at the University of Arkansas Medical Sciences College of Medicine. I am a Ph.D. researcher, and I am a non-voting member. I am the consumer representative.

MS. BROWN: I'm Debera Brown. I'm the Vice President of Regulatory Affairs for Bronchus Technologies. I'm the industry representative and a non-voting member.

DR. WITTEN: I'm Celia Witten, Division Director of DGRND, which is the FDA reviewing division for these products.

DR. MILLER: I'm Michael Miller. I'm Professor of Plastic Surgery at the University of Texas, M.D. Anderson Cancer Center, and I am a voting member.

DR. LoCICERO: I'm Joe LoCicero. I'm a thoracic surgeon. I'm Professor and Chair of Surgery at the University of South Alabama and Director of the Center for Clinical Oncology of the Cancer Research Institute of the

University of South Alabama, and I'm a temporary voting member.

DR. KRAUSE: And I'm Dave Krause, and I introduced myself before. Thanks.

ACTING CHAIRPERSON McCAULEY: I would like to note for the record that the voting members present constitute a quorum as required by 21 CFR, Part 14.

The panel will now hear an update of activities related to the General and Plastic Surgery Devices Panel since the panel's last meeting in February of 2003. The update will be presented by Mr. Stephen Rhodes, Branch Chief of the Plastic and Reconstructive Surgery Devices Panel Branch of the Division of General Restorative and Neurologic Devices.

Mr. Rhodes.

MR. RHODES: Thank you, Dr. McCauley.

I am Stephen Rhodes, the Branch Chief here of the Plastic and Reconstructive Surgery Devices Branch.

Welcome, members of the panel and members of the public and manufacturers to this one-day meeting of the General and Plastic Surgery Panel.

This panel last met on February 28th of this

year, at which time you recommended that a pre-market approval application for a facial augmentation device, Artecoll, be approved with conditions.

FDA continues to work with the sponsor, Artes Medical, on this application.

And in the afternoon you discussed clinical trial issues related to devices designed to treat emphysema.

On March 11th, the agency approved a panel tracked PMA supplement for Inamed's Cosmoderm and Cosmoplast devices. These are injectable implants made from human collagen intended to treat soft tissue contour defects, such as wrinkles and acne scars.

On March 20th, the agency published a proposed rule to classify silicone sheeting for scar management as Class I devices. This panel recommended this classification in our meeting last July.

On June 3rd, the agency published a Class II special controls guidance document for multiple surgical suture devices.

And today you will make a recommendation on a proposed reclassification of absorbable hemostatic agent/devices, and in the afternoon there will be a

discussion regarding clinical trial issues for devices designed for the percutaneous removal of breast tumors.

Panel members, we appreciate your commitment, and members of the public who have requested time to address the panel, we appreciate your comments.

Thank you for your attention.

DR. KRAUSE: Thank you, Mr. Rhodes.

We will now proceed with the first public comment session of this meeting. All persons addressing the panel speak clearly into the microphone as the transcriptionist is dependent upon this means of providing an accurate record of this meeting.

We are requesting that all persons making statements during the open public hearing session of the meeting disclose whether they have financial interests in any of the medical device companies. Before making your presentation to the panel, in addition to stating your name and affiliation, please state the nature of your financial interest, if any, and disclose if anyone besides yourself paid for your transportation or accommodations.

We will begin with those individuals who have notified FDA of their request to present to the open

session.

We have no one. Is there anyone else wishing to address the panel?

(No response.)

DR. KRAUSE: Okay. With that out of the way, since there are no other requests to speak to the open public hearing, we will now proceed with the open committee discussion.

ACTING CHAIRPERSON McCAULEY: No, we have you on the schedule.

DR. KRAUSE: We would begin the discussion of the reclassification of absorbable hemostatic agents and dressings with a presentation of Dr. John Paulson, Vice President of Quality Assurance and Regulatory Affairs, J&J Wound Management, a Division of Ethicon, Incorporated.

His presentation will then be followed by that of Ms. Lene Retboll Muller, who is also the Director of Quality Assurance and Medical Devices, Ferrosan A/S, and then Ms. Judith E. O'Grady, Senior Vice President, Regulatory, Quality, and Clinical Affairs, Integra LifeSciences Corporation.

The FDA presentation and reading of the FDA

questions will then follow these presentations. Then we will have a general panel discussion of this topic followed by more focused panel discussion aimed at answering FDA questions.

Before we complete the reclassification work sheet and supplemental work sheet, we will have a public comment period. Then we will complete the reclassification work sheet and supplemental work sheet.

The vote on these work sheets will actually constitute the panel's recommendation to the FDA.

I would like to remind public observers at this meeting that while this portion of the meeting is open to public observers, public attendees may not participate except at the specific request of the panel.

We will now begin with Dr. Paulson's presentation.

Dr. Paulson.

DR. PAULSON: Dr. McCauley, Dr. Witten, Dr. Krause, and members of the panel, we'd like to thank you for the opportunity to comment today.

It will take us just a moment to get the presentation up on slides.

Per the request to disclose my affiliations, they've been duly noted by Dr. McCauley and are present. I'm an employee of Johnson & Johnson and a shareholder of Johnson & Johnson.

What I'd like to talk about today in a very brief time frame is a summary of the presentation from last year. We noticed that only a couple of the panel members that were present during last year's discussion are here again today. So we'll go over some of the high points that were discussed last year; review briefly the recommendations of that panel; talk about regulatory classifications; and substantial equivalence in Class II regulation implications for products entering the market. We'll discuss special controls which are the centerpiece of regulation under Class II, and recommendations for the panel's considerations.

I'll talk specifically today about Surgicel, although we're here to talk about several different types of absorbable hemostats. Surgicel is a leading product in this category. It is an oxidized, regenerated cellulose product in different physical forms, including fabric, a densely knitted fabric, and a fibrillar material.

It's used adjunctively in surgical procedures

for control of capillary venous or smaller arterial bleeding and rapidly stops bleeding by acting as a matrix for formation of a clot that's readily absorbed from the site of implantation with minimal tissue reaction.

And since we have so many surgeons in the room, I doubt that you need much further detail about this well known product.

Just to briefly mention that the starting material for manufacture of this is cellulose from wood pulp. Wood pulp contains about 50 percent cellulose by mass, and in order to arrive at a purified cellulose, it has to be decomposed essentially and then recomposed into regenerated cellulose, commonly known as rayon, and that's a very common commercial process.

What's not so common is then the oxidation of that product under very controlled conditions with nitrogen tetroxide to form oxidized regenerated cellulose, which as you can see has substituted carboxylic acid functions for alcohol functions at Carbon 6, the glucose molecules which make up the cellulose.

So cellulose is the oxidation reactant. The major reaction product is ORC, oxidized regenerated

cellulose, which you see on the left. But there are also a number of other reaction products which turn out to be significant in some regards.

I call your attention to the two and three ketone ORCs at the top of the slide, and while the efficacy of ORC is typically related to the main reaction product, we understand from recent publications that the two and three ketone ORCs are controlling in respect to degradation in the body so that the biological absorption of the body is related to the two and three ketones.

Okay. I'm going to briefly talk about some of the mechanisms of action of Surgicel, the physical and chemical attributes which control it, and the ways in which they're governed by existing standards and specifications for Surgicel. And I'll call your attention to the multiple mechanisms of action that are listed on here, which include physical and mechanical actions in tamponade, food absorption, swelling and gel formation, and then surface interactions with proteins, platelets, intrinsic and extrinsic pathway activation.

These are associated with physical and chemical properties of Surgicel which are listed in the column in the

middle, and then if we refer to the U.S. Pharmacopoeia, a common reference for attributes that control pharmaceutical products, which is how this product was originally approved, we see that USP specifies none of the physical and mechanical properties listed here. It describes only some of the chemical properties noted under surface chemistry.

So those attributes are in relation to hemostasis. In relation to biocompatibility, and important consideration since this is, in effect, an absorbable implant which is frequently left behind in the body, I've mentioned just a few toxicity endpoints that are of importance. I've mentioned some of the Surgicel properties that relate to these toxicology endpoints, and I've shown here the USP requirements for these elements that are important to biocompatibility.

And the point of these two slides is to say that there are important biological interactions of these products that are controlled by physical and chemical properties, but not well described by U.S. Pharmacopeia requirements or other standards.

Those of you who use U.S. Surgicel get a consistent product. We are, in fact, the only manufacturer

of oxidized regenerated cellulose product in the United States, but there are products which claim to be ORC and in some cases are ORC from different parts of the world.

This is Cellulostat from China and Taiwan. It says it's oxidized regenerated cellulose.

This is ORC from Europe, a product called Curacel, and here is some analysis of these products, and you can see that I've highlighted in yellow and italics some differences among these products that could be clinically important or may just be chemically important, but there are differences among the products that you can see.

And I've also lined up in the column on the far right the USP specifications for these, and you can see the areas where it is controlled and some areas of differences where USP requirements do not provide controls.

I'll call your attention particularly to Cellulostat, which claimed to be ORC, but according to spectoral identification and identification tests, it does not appear to be ORC at all.

As we evaluate products in the laboratory, we use a standardized swine spleen incision model using a standardized incision. We use digital compression and

measure time to hemostasis.

Here you can see Surgicel nu-knit applied. You can see that there is a fluid absorption, hemoglobin oxidation which causes a darkening of the material and gel formation or false clot under which true clotting occurs.

We use this model to compare our own products with other products and to study innovations in this area.

Here we're showing some of the time to hemostasis results that are achieved when we compare products. Surgicel nu-knit, as I mentioned, is a heavier, denser knit of product that achieves hemostasis in approximately three minutes. Two replicates with Surgicel demonstrate hemostasis in about eight minutes, Curacel in approximately ten minutes, and Cellulostat failed to achieve hemostasis in greater than 12 minutes.

And so we believe that this model, which is reasonably standardized and a good indicator of effect on blood clotting, does indicate that there are meaningful differences in performance among these products.

This slide is here just as a reminder that we're dealing with oxidized regenerated cellulose, which I told you absorbs with minimal tissue reaction in a very brief

period of time. Cellulose itself does not absorb from the body. The body is incapable of breaking down cellulose and results in chronic inflammation and nonabsorbed material.

Here's a cut and suture two years after implantation, and you can see the inflammation. This is put in here to call to attention that cellulose itself, were it to be in completely oxidized, were it to be unabsorbed, is undesirable for an object. It does not perform or absorb from the body, and as surgeons, you're well aware of its adhesiogenic and inflammatory properties.

Okay. Last year, in summary, of the information that we provided last year, Surgicel is, indeed, an absorbable hemostat that has a long history of safety and effectiveness, as I'm sure Dr. Krause will tell you. It has complex chemistry and processing, which create unique product properties, multiple physiologic interactions required for safety and effectiveness, and that other ORC products are not equivalent in terms of time to hemostasis, physical properties and chemical composition.

And finally, the recognized standard existing in the marketplace, the U.S. Pharmacopeia, does not address many critical product attributes.

At last year's advisory panel meeting, the panel was concerned about the divergent nature of the technologies. We're talking right now about Surgicel, which is derived from cellulose. Other presenters will talk to you about gelatin and still others about collagen products.

These are very divergent products in terms of their nature, chemistry, and potential impacts on surgery. There are issues about inequality of products that I've just reviewed with you and control over complex product attributes.

Last year the panel voted four to three to table the action on reclassification and requested FDA to work with industry to develop guidance and address concerns, and they requested that this guidance document be returned to the panel for review before reclassification recommendation was made.

Briefly I'll go through classification, which I'm sure Dr. Krause will do. Class I is not under consideration here. It's the class of products where general controls, such as good manufacturing practices or quality systems regulations are sufficient to reasonably assure safety and effectiveness.

Class II products are those where reasonable assurance of safety and effectiveness require general controls, including pre-market clearance and design control, plus some or all of the following. I particularly call to your attention development and dissemination of guidelines, including possible clinical data requirements and others which are listed.

Class III, the class in which these products currently exist, are not in Class I due to their medical importance and cannot be assured safe and effective on the basis of general controls and not in Class II because insufficient information exists to assure safety and effectiveness using special controls.

We argued last year that because the U.S. Pharmacopeia did not provide a full spectrum of requirements in key areas for this product that this product should remain in Class III, but I think that was not necessarily the sentiment of the panel here, and the issue that came back is defining the special controls that were needed to assure these products remain safe and effective in the future.

Under Class II regulation the process of market

entry is decided on the basis of substantial equivalence. The types of changes which occur under Class II regulation include changes in chemical composition, physical form, indications for use, contraindications, instructions for use, performance specifications, and methods of manufacture and sterilization.

So unlike the movement of a prescription pharmaceutical that's unique and innovative to a generic form where the chemistry, indications for use remain identical, that is not necessarily the case as we move from Class III to Class II in devices. Substantial changes to these products and their uses can be anticipated and should be anticipated in preparing this guidance document.

We believe there are also issues about indications for these products versus data. Surgicel has been on the market for more than 40 years, was originally supported by clinical studies involving over 500 patients in numerous surgical specialties, and subsequently there are hundreds of published reports of Surgicel in a variety of surgical procedures, all of which combine to provide assurance about its safety and effectiveness.

Its indication for use is surgical procedures,

and as we proceed now to begin to consider substantial equivalence, this raises questions about what does it take to be substantially equivalent to a product who is indicated in the world of surgical procedures.

These are some specific surgical uses of Surgicel supported by clinical data. They include neurological, cardiac including grafts, vascular including grafts, gynecologic, orthopedic, abdominal, thoracic, ENT and others.

While all of these represent hemostasis controls, when you get beyond hemostasis, there are procedurally related controls, some of which I've listed. For general surgeons, we have tissue response absorption, adhesions in wound healing. In neurologic, we have neurotoxicity; pyrogenicity since the central nervous system is especially vulnerable to bacterial pyrogens; tissue reactions, absorption, adhesions, migration, compression of nerves and vessels due to product swelling in confined spaces.

In cardiac and vascular surgery, we have a tendency to rebleed, tissue response, compatibility and effectiveness with grafts and sutures, adhesions and fistula

formation.

In gynecologic surgery, consider if you will just ovarian tissue response and adhesions which are very important in preserving reproductive capability.

With orthopedic surgery, tissue response, absorption, cyst formation, interference with bone formation are items that are already listed in labeling for these products, but need to be considered carefully as we think about future products that may be dissimilar in the regards I mentioned earlier.

In ophthalmic, we have tissue reaction, postop. response, plus neurologic concerns, and in urologic surgery, efficacy in the presence of urine, absorption, urethral and ureteral obstruction, and calculus (phonetic) formation.

And the point of going through this is to say we've got these very, very broad indications. Yet when you get to specific surgical uses, there are unique and special attributes and performance requirements that come into play.

So with all of this in mind, what are some considerations? We've got diverse materials and technologies, broad indications in general surgery and surgical specialties. These are critical medical

applications, considered neurosurgery and cardiovascular surgery, as well as all of those that I've mentioned.

These are implantable, absorbable materials of biologic origin, and we can anticipate significant change in future products.

Our recommendations are that indications be limited to those with adequate data provided rather than all established uses of products with a long history of safety and effectiveness. I don't know of any other category of products that could gain an indication as broad as the one we've just reviewed without substantial data in the relevant specialty surgeries.

We believe that specialized biocompatibility studies related to the tissues and uses in surgical specialty are advisable and should be required and that clinical studies in the general surgery and the individual surgical specialties, for example, neurologic, cardiovascular and gynecologic, studies should be conducted as part of the substantial equivalence demonstration.

Thank you.

ACTING CHAIRPERSON McCAULEY: Are there any questions for Dr. Paulson?

(No response.)

ACTING CHAIRPERSON McCAULEY: We will now move on and hear the presentation by Ms. Muller.

MS. MULLER: Good morning. My name is Lene Muller, and I'm representing Ferrosan. It's a Danish company, and we have our products distributed here in the U.S.

And with regards to the economical interest, I'm an employee at Ferrosan in Denmark.

And I'd like to thank the committee for giving me the opportunity to represent Ferrosan at this FDA hearing.

I hold the position as Director of Quality Assurance and Regulatory Affairs at Ferrosan A/S.

The objective of my presentation is to go through the most critical factors of absorbable gelatin based hemostats; to touch briefly on the safety profile or surgical and spongosinal (phonetic) products; and have a look at the existing controls in the USP, Pharmacopeia; and also address issues of consideration for future regulation or guidance.

The products that are manufactured by Ferrosan

is the spongostinal (phonetic) products which is absorbable gelatin sponge which we've been producing since 1947 for the European market, and recently in 2002, we also launched Spongostan powder for the CE market.

In the U.S. market, we have surgical products, which is absorbable gelatin sponge USP, which is PMA approved back in September '99.

We also have surgical powder, and the PMA supplement was approved in September last year.

Does Ferrosan find a reasonable assurance for safety and effectiveness for absorbable gelatin based hemostatic agent as a Class II device? Well, the answer is for the existing product, yes, due to the massive documentation that is in place, due to the PMA registration and the registration we have in the rest of the world.

For similar or new products or new materials we don't find this same to apply.

You can ask the question: why is the safety profile for this type of product very good? And there are some answers to that, and I think one of the very important ones are the clinical and the animal studies, and those are the toxicity and the biocompatibility.

We also have controls of the animal derived raw materials and the manufacturing processes, and this is dues to many years of experience and very thorough knowledge both in production and in use.

When we look at some of the most critical factors for absorbable gelatin based hemostatics, well, the effectiveness of the product is well documented through clinical studies, and the toxicity and the biocompatibility has been conducted in animals with satisfactory result.

And the raw material controls includes a risk assessment of infectious materials due to the animal origin of the material, and I think that's a very important part when you deal with raw materials of animal origin because we are all aware of the possibility of viral activity or prions.

And finally, I've mentioned that absorbable gelatin Spongostan and power are sterilized and packed in material that provide a sterile barrier, and that, of course, goes for a lot of other medical devices.

But I think the three top are the most critical factors for the absorbable gelatin based hemostats.

When we look at gelatin as a material, we know

that it's very sensitive to slight changes in the manufacturing or sterilization process, which could create varying product characteristics which lead to product performance issues. It could be a tendency to swell or absorbency.

When we look at the products prior to, for instance, sterilization or different types of sterilization or different types of sterilization cycles or the power used for the Epping sterilization, we know that it affects the absorbency of the gelatin products.

We are all also aware of some of the other products on the market. There is instances where formaldehyde is used. We know they're used to harden the product of the absorbable gelatin sponge, and I think that is a very important implication for tissue compatibility.

When we look at the PMA application that we made, we had performed clinical investigation for Surgifoam absorbable gelatin sponge USP prior to the FDA approval. We performed the clinical investigation at multi-sites with 281 patients involved, and the clinical investigation included general surgery, cardiovascular surgery, and orthopedic surgery, and was also compared to an existing hemostatic

agent.

The safety and effectiveness for neurological use has been supported by a study involving 700 cases in the EU. Also we've performed animal studies using the spinal model for comparing Spongostan and Surgifoam to the existing product.

We've performed a wide range of toxicity and biocompatibility studies that are listed here, all with satisfactory result.

We also conducted a risk assessment of the raw material due to the animal origin, and we find that the anti-infectious treatment of the Porcine raw material during the extraction of the raw material is very important.

We also do a very careful selection of raw material sources and processing. All of the herds and animals are under very careful veterinarian control and surveillance.

We have traceability from the animals to the raw materials, and we also do vendor surveillance and audits.

When we receive the material, we go through a very thorough receipt control.

Based on these critical factors, Ferrosan

handles and regards the absorbable gelatin based products in line with our pharmaceutical products. We tend to handle them in the same manner.

The product development and the manufacturing is performed in compliance with the FDA quality system regulation, including design control.

Our manufacturing site is in Copenhagen, Denmark, and it is FDA registered. We also have had an FDA pre-approval inspection, and we have routine inspection by the FDA. We send in annual reports and PMA supplements for changes.

When you look at Spongostan and Surgifoam absorbable gelatin sponge safety profile, we have a history of more than 50 years of safe use of Spongostan in Europe. The adverse event per sold unit is very low. It reflects actually three cases in more than 300,000 sold units, and so far we have had no product recalls.

However, we think and believe that some of this is due to the current stringent controls and the clinical validation prior to the FDA approval.

When you look at the controls in place right now in the USP, when you look at the gelatin raw material

monograph, it is from the national formula, and the monograph is intended to use for gelatin used in manufacture of capsules or tablets.

Some of the parameters listed here are relevant also for the implants, but I think that if the monograph should reflect the purpose of this type of use of gelatin, there could be other things to take into consideration when you're thinking of the animal origin as an implant.

These are the parameters that are included in the USP monograph for the Finnish product, the absorbable gelatin sponge, and I think that that doesn't cover all of the critical factors that I just brought to your attention previously.

When you look at some of the issues that we think that is necessary to take into consideration, it is the design control, especially the clinical trials and the animal studies, the toxicity, the biocompatibility, and the risk assessment of the origin of the animal raw materials, special labeling, physical performance including water absorption, swelling, digestibility, reconfirmation, dimension, and density, and also the stability studies.

My conclusion is if the reclassification is

being implemented, I think that identical materials, if not processed in the same manner, may have varying product characteristics, and additional special controls are deemed to be incorporated in the guidance to cover the critical factors, especially with regards to effectiveness and the animal origin.

Thank you.

ACTING CHAIRPERSON McCAULEY: Are there any questions for Ms. Muller?

(No response.)

ACTING CHAIRPERSON McCAULEY: Thank you, Ms. Muller.

We'll now move on to the presentation by Ms. O'Grady.

MS. O'GRADY: Good morning. My name is Judy O'Grady. I'm the Senior Vice President of Regulatory Quality and Clinical Affairs for Integra LifeSciences Corporation.

I'd like to thank Dr. Witten, Dr. Krause, and other members of the Food and Drug Administration, Dr. McCauley as Chairman, and other members of the General and Plastic Surgery Devices Advisory Panel for allowing me the

time to speak at this public advisory committee meeting regarding reclassification of transitional Class III devices, the absorbable hemostatic agents and dressing devices intended to hemostasis during surgical procedures.

The objective of my comments today is to give a brief summary of the presentation and comments made to this advisory panel in July of 2002 and recommendations to FDA for issuance of final guidance document for special controls for transitional Class III devices, absorbable hemostatic agents if reclassified to Class II.

In summary of the comments that were presented, absorbable hemostatic agents, the current classification in FDA and the United States is they're classified as Class III pre-market approval required, which is a PMA. In the European Union the classification is the same. They're Class III, and this is due to the fact that the devices have a biological effect or are wholly absorbed or mainly absorbed.

Devices that are in direct contact with the CNS, heart, and major vessels, and all devices manufactured using products of animal origin are placed in the same category.

In Canada, they have a similar classification in

the European Union and as well as FDA. They are surgically invasive, intended to be absorbed in the body, and again, any type of medical devices incorporating products of animal origin.

In Japan, a similar classification and data requirements of the FDA and EU, as well as a clinical trial is required.

Australia, again, similar classification data requirements as FDA and the EU, and the rest of the world, most countries have very similar classifications for any absorbable hemostatic agents, and in fact, some countries classify absorbable hemostatic agents as pharmaceuticals.

Some of the data that was submitted to FDA in support of PMAs for absorbable hemostatic agents, full line of biocompatibility studies. I'm not going to read all of these, but there were some specialized studies, specifically genotoxicity studies, also studies looking at the immunogenic potential. Many implantation and absorption studies, and then additional testing, such as mechanical testing, swellability, compression, and that is if these products are going to be used around vessels or in and around the spinal cord so that as they absorb fluid, that

they don't apply any type of compression.

And then if it's a product of animal origin, viral safety studies, as applicable.

Animal studies, implantation studies evaluating rate of absorption, foreign body reaction, incidence of infection, incidence of adhesion formation, and incidence of any other tissue reaction, and hemostatic studies in an animal model.

Clinical trial data. There have been multiple clinical trials conducted on these product lines. Some studies have involved up to 550 patients looking at general cardiovascular, neurosurgical, OB-GYN, urological, burn and plastic surgery procedures and the controlled population being of other marketed hemostatic agents.

Some of the parameters that were evaluated during these studies were time to hemostasis, adherence to the site, pliability, handling, overall performance, and then looking at postoperative bleeding, hematoma formation, and postoperative evaluation evaluating adverse events.

Manufacturing. These products are manufactured in compliance with FDA quality system regulations, which are good manufacturing practices. Facilities, FDA registered,

ISO 9001 certified.

Since these products are PMA products, pre-approval inspection is required, and also there's routine inspections of the manufacturing facility for compliance with FDA quality system regulations.

Annual reporting requirements to the PMA and PMA supplements for any significant changes to the process, procedures and testing of the products.

Recommendations to FDA regarding reclassification. Recommend strongly that if FDA reclassifies absorbable hemostatic agents from Class III to Class II, that it includes special controls. Class II devices are defined in Section 513 of the FD&N Act to include any devices for which reasonable assurance of safety and effectiveness can be obtained by applying special controls.

Only general controls will apply to Class II devices unless special controls are established by regulation. Special controls may include special labeling requirements, mandatory performance standards, patient registries, post market surveillance.

Reclassification should only occur with issuance

of an FDA final guidance document to assure continued safety and effectiveness profiles. Current FDA approved PMAs, PMA supplements remain in place and viable, and that the confidential information, such as manufacturing data, remain confidential, not available for release under FOI.

Guidance documents should include, of course, standard information and description of the devices and the principle of action of each of the device components. If collagen is a component of the hemostatic agent, it should comply with FDA guidance document in medical devices containing materials derived from animal sources.

Looking at the type of collagen, tissue, and species, country of origin, processing of the collagen, viral inactivation studies, and the BSE/TSE risk analysis.

Biocompatibility testing should be in accordance with FDA guidance. Use of international standards, ISO 10993, looking at the battery of biocompatibility studies, but also including mutagenicity studies, immunogenic potential, biodegradation studies, and other studies as indicated by the type of biomaterial.

In vitro as well as in vivo hemostasis studies.

Preclinical studies should also include

implantation to look at the rate of absorption, foreign body reaction, incidence of infection, incidence of adhesions, and incidence of any other tissue reaction.

Clinical experience. There should be a summary of any clinical experience. The sponsor should demonstrate that the hemostatic agent will perform as safely and effectively as another legally marketed absorbable hemostatic agent.

Clinical data for hemostatic agents composed of materials for which have not been previously used as implantable, absorbable hemostatic agents should be provided from a multi-center clinical trial.

Clinical data should be obtained for high risk surgical procedures where postoperative bleeding adverse events are especially critical, such as neurosurgery, ophthalmic surgery, and others as indicated.

Clinical data should demonstrate that hemostatic agent performs similarly when compared to another legally marketed hemostatic agent.

Clinical studies should evaluate if indicated time to hemostasis, days of adherence, ease of handling, and critical, which would be postoperative, evaluations of

postoperative bleeding, infection, hematoma formation, wound dehiscence and any adverse events.

Sterilization should include the method of sterilization validation studies. A sterility insurance level of ten to the minus six, and description of the monitoring of the sterility for each lot and description of the packaging or the product to maintain sterility.

Again, on sterility, if radiation sterility, the dose should be indicated. If the method is ethylene oxide sterilization, the maximum levels of ethylene oxide, chlorohydrin, and ethylene glycol residues which remain in the device should be identified and comply with the maximum limits proposed in the Federal Register and also in AAMI, ANSI, ISO guidance document 10993.

Pyrogenicity testing. The pyrogen level of the final sterile device should be less than .06 endotoxin units per mL, and this is specifically for any neurosurgical use or in contact with cerebral spinal fluid.

Product expiration testing, data should support the expiration date for the product and should be submitted, and stability studies should monitor the critical parameters of the device to insure that it will perform safe and

effectively over the lifetime of the product.

Manufacturing should comply with FDA quality system regulations, including design controls. Submission should contain information on the device reagents and processing, device specifications, product release testing, residual levels of manufacturing agents, such as any leachables, residual levels of heavy metals, pyrogen levels, packaging, sterility.

Summary. Reclassification from Class III to Class II should only be with special controls and an FDA guidance document in place to insure continued safety and effectiveness profiles. The current approved FDA PMAs for absorbable hemostatic agents should remain in place.

Specialized clinical and preclinical studies should, at a minimum, address concerns related to use and surgical specialties, such as neurosurgical, cardiovascular, and other specialized procedures.

Thank you very much.

ACTING CHAIRPERSON McCAULEY: Does the panel have any questions for Ms. O'Grady? Yes.

DR. LoCICERO: Your company has made a specific recommendation for pyrogenicity level for neurologic use.

Do you make recommendation for pyrogenicity levels for other uses?

MS. O'GRADY: Yes, I do. The pyrogen level, I know the collagen hemostatic agents manufactured by a company all meet the level for neurosurgical use, which is .06 endotoxin units, but I believe there could be some other requirements if the product was not going to be used in neurosurgery for endotoxin units. But they all should be nonpyrogenic.

ACTING CHAIRPERSON McCAULEY: Are there any other questions from the panel?

(No response.)

ACTING CHAIRPERSON McCAULEY: We will now hear the FDA's presentation.

Thank you, Ms. O'Grady.

MS. O'GRADY: Thank you.

ACTING CHAIRPERSON McCAULEY: We will now hear the FDA's presentation by Dr. Krause.

DR. KRAUSE: Before I start, I'd like to welcome all of you, especially Dr. McCauley, panel members, Dr. Witten, attendees from industry, attendees from the FDA and all other attendees who have taken their time to attend this

meeting of the General and Plastic Surgery Devices Panel.

My name is David Krause. As well as being the Executive Secretary of this panel, I'm a reviewer in the Plastic and Reconstructive Surgery Devices Branch in the Division of General Restorative and Neurological Devices, and I have been the lead reviewer on quite a few PMAs for the absorbable hemostatic agents.

Today FDA would like the panel to consider reclassifying the absorbable hemostatic agents from Class III to Class II.

Okay. Basically I will focus on the following topics. I'd like to begin with a general definition of absorbable hemostatic agents as it is now in the 21 CFR. I'd like to go on to FDA's beliefs as to why Class II would be appropriate for hemostatic agents. I'd like to give a brief history of absorbable hemostatic agents and summarize what was the panel's recommendation at the last panel meeting.

I'd like to then discuss special controls document, present MDR reports, and what risks FDA feels need to be addressed, and finally, give you FDA's proposal for the absorbable hemostatic agents.

The 21 CFR, which is the Code of Federal Regulations, at this time defines absorbable hemostatic agents as a device intended to produce hemostasis by accelerating the clotting process of blood, and then it says it is absorbable, and it's presently Class III.

That's a pretty nebulous and very general description of the hemostatic agents, but I think it's intentionally so, so that products that fit that general description can be looked at for the use as a hemostatic agent.

FDA believes that the reclassification to Class II is appropriate for a number of reasons, but the two most important and, I think, the most appropriate or clearest reasons are these two, which basically are that the device specifications and the performance characteristics, which includes bench testing, animal testing, and clinical data that are needed to evaluate and control the safe and effective use of these devices, are well understood after years of experience.

Secondly, down classification meets the FDA's mandate to apply the least burdensome approach to regulating medical devices. One of the factors that's taken into

account when the FDA considers Class I, Class II, or Class III or a number of the factors is kind of a combination that includes, number one, the risks associated with the device, but also the experience, and there are devices that are Class III and require a PMA that are not very risky devices, but how they work is not very well understood.

These devices, how they work, you know, with the length of time that they've been around are fairly well understood by the industry as well as the agency when it comes to regulation.

A brief history of the absorbable hemostatic agents is that up until the device amendments were signed by President Ford in 1976, these were regulated as drugs. They required a new drug application to the Center for Drugs and were reviewed as drugs and those types of studies that the Center for Drugs would use were the types of studies that were done in order to assess these products.

After the signing of the device amendments, a number of devices -- I think there were about 16, but I'm not sure -- were transferred to the Center for Devices, and most of them I think wound up in Class III for regulation via pre-market application or what we call a PMA. The

hemostatic agents were one of those.

If you look back through history and you look at the products that have been marketed in the United States as absorbable hemostatic agents, Oxycel, Surgicel, Avitene, and Gelfoam have the oldest applications. Oxycel and Gelfoam have been on the market the longest, both since the early to middle '40s. Surgicel was approved by the Center for Drugs in 1960. Avitene was approved in 1976.

But all of these, as you can tell by the N number, were submitted to the Center for Drugs as new drug applications.

Later, as the Center for Devices began to regulate these products, you notice the P numbers appear, and Avitene, another form of Avitene, Collastat, Superstat, Instate were the earliest products to go through the PMA process at the Center for Devices.

These were followed closely by Helistat, Novacell (phonetic) or Novacol -- excuse me -- Hemostagin and Surgifoam, and finally FloSeal and CoStasis.

Oxycel, which was on the first slide, is no longer being sold in the United States. Superstat is also no longer being marketed in the United States. Hemostagin,

which was on the slide previous to this one, is no longer being marketed, and an interesting fact about these two products is that both of these incorporated the licensed bovine thrombin as part of this product. So these were -- the FloSeal matrix and CoStasis, both included thrombin as a component, and they both used the licensed form of bovine thrombin.

There was a panel meeting July the 8th, 2002 -- I'm sorry. It says 2003 up there -- which discussed this topic. At the time the discussion on reclassification was tabled so that a contents of a guidance document could be evaluated.

Each of you have got basically what we would intend to put into such a guidance document in the memo that we sent you, as well as posted on the Web for anyone else to look at.

Basically the purpose of a special controls guidance document is to express or to convey to industry what is the current thinking within the agency at this time. These types of documents are subject to updates, and they're not considered requirements per se, but they do lay out the kinds of information that the agency believes needs to be

provided in order to establish substantial equivalence.

In general, a special controls guidance document would be laid out as I've shown here. We've provided you with the suture guidance document as kind of a guide, and if you noticed, it was slightly different, and you know, these undergo constant modification as to how the agency thinks these sections should be labeled and, you know, types of information.

But each update is intended to be better than the last. So hopefully it happens that way.

Section 1 would be where general information, including a brief explanation of why the guidance document has been written, a device for which the guidance document has been written, references to the Federal Register. It identifies previous guidance documents that are superseded by this guidance document and things like that would be in Section 1.

Section 2 would be where the FDA believes that special controls combined with general controls are sufficient to provide reasonable assurance of safety and effectiveness and includes a brief summary of other sections by stating where you would be able to find information on

regulations, risks, things like that in the guidance document.

Also, the background section would identify Web sites and other guidance documents that would give advice on the submission of a 510(k), including a rationale for least burdensome approach to device regulation.

The third section, which is the content and format of an abbreviated 510(k) submission, is a boilerplate section which only talks about abbreviated 510(k)s and really wouldn't apply to this type of a 510(k).

Section 4 is the scope section where it identifies products, regulations, the product codes, and other things that are specific to this particular product type.

Section 5 of the guidance that we're proposing for the absorbable hemostatic agent products at this time would be the section where we would list the risks to health. Here FDA would identify the specific risks to health that are generally associated with the use of an absorbable hemostatic agent and also identify the measures that are recommended to mitigate these risks.

In a few minutes I'll be addressing risks and

mitigation, and you'll see that table there.

Section 6 is a very detailed section which discusses the material and the performance characterization, and I don't want to go through that in great detail. That's in the handout that we had sent you and the one that we posted up on the Web, but I think the industry representatives did a really good job of pointing out the types of criteria that would go into that section.

Basically it would talk about material or information on the material itself, you know, the exact questions that were posed. You know, is the herd regulated? What are the BSE/TSE, you know, transmissible agents, viral inactivation? Are all of those things addressed? That would be in that particular section.

There would also be manufacturing information which would take into account the types of information that Dr. Paulson was talking about with Surgicel, where the pH and the degradation of the material and all of those types of things would be monitored through careful studies and would need to be submitted in a 510(k) to let us see, you know, that that information is understood.

Sterility, the USP definition, does or does not

the product meet that? Those types of things would all go in that section.

Final device information, is it cross-linked? Is there a cross-linking agent? How much? How much is residue?

For instances, some of the older hemostatic sponges maybe have been cross-lined with glutaraldehyde. So some glutaraldehyde information would then be necessary because everyone knows that glutaraldehyde is toxic.

Shelf life information would go into that section, et cetera. These would be all of the pre-clinical types of bench top testing data that would be assessed in Section 6.

Section 7 would deal with animal testing, and here for example, I can just read you what's in there at this point. It says, "FDA recommends that you provide animal studies modeling each surgical application for which the absorbable hemostatic agent is to be indicated. For example, for general surgical use, we would recommend that animal testing include arteriolar, venous and capillary bleeding from various tissues and organs. For the arterial bleeding we recommend that you provide specific data to

support this indication."

And then other similar indication we would want people to monitor infections, hematomas, coagulopathies that are as a result of the use of the hemostatic agent, increased wound healing times, et cetera. That's the type of information that we would want to see in the animal testing section.

Finally, Section 8 deals with clinical testing, and there's a long list of the types of information that we would be looking for there. I'll just go through a little bit of it.

It says, "A clinical study should be designed to compare the safety and effectiveness of the new device to a legally marketed predicate device. In most cases such comparisons should be made between absorbable hemostatic agents manufactured from similar materials with similar indications for use."

So if somebody were manufacturing a device made of regenerated oxidized cellulose, considering that there's only one on the market in the United States, we would expect to see clinical data comparing that new product to the predicate product, which in that case would be Surgicel.

Also, a study should be conducted at enough institutions to assure that the observations made regarding the safety and effectiveness of the devices will be significant in spite of technical and procedural differences likely to be encountered when the device is marketed. And that section goes on and gives basically that type of advice.

Section 9 of the guidance document at this time is the section on sterility, which is a boilerplate section which basically refers to guidance documents that are in existence for how to assess sterility and to, you know, validate, et cetera.

I think Ms. O'Grady did a really good job of covering the kinds of information that that guidance document asks for.

Biocompatibility is also boilerplate. It refers to the same document that Ms. O'Grady pointed out, which is the ISO 10993. The section on labeling, again, is boilerplate. It includes the suggestions for prescription use devices, that they must carry the statement caution "federal law restricts this device to sale by or on the order of a physician." In most cases these would be being

used in the surgical theater. So it's not really something that's going to be sitting on a shelf in a drugstore.

And the other advice is given on instructions for use, and the instructions should include adequate information regarding the contraindications, warnings, and precautions in order to address the identifies risks to health and a clear explanation of the device technological features and how it is to be used.

And as a sample of that type of labeling, I gave you the labeling for Surgifoam, which was discussed in one of the previous industry presentations so you have an idea of the type of labeling we'd like to see for these devices.

In preparation for this discussion, I reviewed the MDR reports as listed in the FDA tracking system, and it's important to note that up until 1992 there was no real tracking system. Beginning in 1992, the tracking system was voluntary up until 1996 at which it became mandatory that medical device failures, events that were a problem were reported to the FDA.

So you know, you can guess that a lot of this information is under reported. However, I think what I'm pointing out to you here is what's been reported to the FDA,

and when you consider that there probably have been millions of uses of these devices during this time, there is an amazingly small amount of what we call medical device reports which report problems with the device as perceived by those using them, you know, surgeons, hospital staff, et cetera.

This list is complete up until June 13th, 2003, which is when I accessed the system to get the data.

There were more than the 59 reports that I have here, but as I read through them carefully, I noticed that some of them were for bone wax, which is not considered an absorbable hemostatic agent. It doesn't have the same product code. At this point it's an unclassified device that's somewhere else, but I think by mistake some of those were put down here. So those I eliminated.

And I also eliminated devices which were used for femoral artery closure which have their own product code and somehow got lumped in with these. I think there was maybe like 50 of those, and I'm not sure why they put in there, but I went through and I weeded those out.

And so this is what I came up with, which it could be off by a few in either direction, but I think it's

a fairly good estimate of the MDRs reported, and you can see hemostasis failure up until a couple of years ago, there was only one reported, and the most recent ones, I think, is people expect more from these newer hemostatic agents, and they are trying them on a lot of places where they before wouldn't have used them, and so I think there are a few more failures in the last couple of years.

Deployment failures, those are basically the person can't figure out how to put the thing together. So I thought that was interesting. That's one of the main ones. So that's not really a problem with the device. It's a problem with somebody being all thumbs, you know, like Richard Nixon or something.

Abdominal infection, sinus infections, paralysis. In most cases this is probably due to off-label use. Most of these products are labeled very carefully that you shouldn't stick them in small spaces because they swell, and these are probably where people did just that. They stuck them in small places. The device swelled. There was some nerve damage and paralysis follows.

Oral infections, granulomas, abscesses. As you can see, there's very few of these reported.

Additionally there were a number of other foreign body reactions, allergic reactions, et cetera, you know. Like I said, I found a total of 59, and I could be off by ten either way, but I think it's a pretty accurate portrayal of what's out there in the MDR system.

Okay. By searching the literature, going through the MDR reports, reading through the labeling for absorbable hemostatic agents that are presently marketed, and also looking through the SSEDs of PMAs that are in our files and on record, I was able to identify the following potential risks, and basically we are proposing the control that's in the right-hand column.

So for uncontrolled bleeding we believe that animal studies and/or clinical studies can be used to assess the hemostatic capability of the products, hematoma formation, again, animal studies, product labeling, infection and fever, animal studies, product labeling, sound dehiscence, product labeling, foreign body reaction, inflammation, edema, granuloma. As you can see, these are some of the proposed methods.

Adhesion formation, failure to be absorbed, interference with methyl methacrylate adhesion. That's kind

of an old one that's been around for a long time if you go through the labeling of these devices. It turns out that some of the collagens may inhibit the adhesive properties of the methyl methacrylate.

Aspiration into transfusion filters, and we believe most of these or a lot of these can be addressed with product labeling.

Product failure due to anticoagulation therapy. Again, that's something that can be assessed or at least surgeons who are going to use the product can be warned in the labeling that they should be careful if the patient is on anticoagulation therapy.

Some of these devices actually work quite well on patients who are on anticoagulation therapy, but still it's a good warning to make doctors, surgeons keep an eye on patients.

Others were, you know, using in small spaces; the possibility of embolization if somehow accidentally the device is injected into a blood vessel. Device swelling, allergic reactions, again, those all can be controlled for.

Products with thrombin. Every product that has thrombin in it has a large boxed warning, and the boxed

warning is a recent addition to thrombin, and it's because the potential for cross-reactivity of antibodies that are made to the bovine factor Va cross-reacting with the human factor Va and the coagulation cascade and thus resulting in a potential coagulopathy.

In the two products that we looked at that had thrombin, we saw none of this, but we do require the boxed warning to go on the label for people to be on the lookout for this.

And the second additional risk was all of the problems that we saw where people were complaining that they couldn't put the devices together were for the two latest PMAs, which were syringe type devices that required some putting together and apparently they didn't read the instructions or whatever and couldn't put the device together, but it's not a big deal.

So the FDA's proposal is that the absorbable hemostatic agent product be reclassified to Class II, and we are recommending a special control, and in this case it would be a detailed guidance document.

The present listing for absorbable hemostatic agent is the one I read you the definition before. It's

Class III, requires a PMA. The proposed new identification would be absorbable hemostatic agent, surgical. The definition would remain the same, and it would be Class II with the special control guidance document as previously indicated.

That's the end of my presentation. During your discussion these are the questions that we would like you to discuss, and we can read them later when you get to that discussion.

If anyone has any questions, I'd be glad to answer them.

ACTING CHAIRPERSON McCAULEY: Are there any questions from the panel for Dr. Krause?

(No response.)

ACTING CHAIRPERSON McCAULEY: Dr. Krause, will you now read the FDA questions? We will not address the questions at this time, but will address them in our later deliberation.

DR. KRAUSE: Okay. The questions are as follows:

Please discuss the proposed reclassification of the absorbable hemostatic agent and dressing products.

Please also discuss what descriptive information and intended use should be included in the classification identification.

Second, please discuss the risks to health for the absorbable hemostatic agent and dressing devices.

And, third, are there any other risks to health for these devices that have not been identified?

Thank you.

ACTING CHAIRPERSON McCAULEY: Thank you, Dr. Krause.

This is a good time to take a break. We'll come back in 15 minutes.

(Whereupon, the foregoing matter went off the record at 10:02 a.m. and went back on the record at 10:25 a.m.)

ACTING CHAIRPERSON McCAULEY: We will now proceed with some additional time for open public comment. All persons addressing the panel speak clearly into the microphone as the transcriptionist is dependent upon this means of providing an accurate record of this meeting.

We are requesting that all persons making statements during the open public hearing session of this

meeting disclose whether they have financial interests in the medical device company before making a presentation to the panel. In addition to stating your name and affiliation, please state the nature of your financial interest, if any, and disclosure if anyone besides yourself paid for your transportation or accommodations.

Are there any individuals wishing to address the panel at this time?

(No response.)

ACTING CHAIRPERSON McCAULEY: Since there are no other requests to speak in the open public hearing, we will continue with the open committee discussion and the FDA questions.

We will start with the panel deliberation portion of this session. Are there any comments currently from the panel?

Dr. Miller, do you have any comments you would like to add at this time?

DR. MILLER: I think I was present for our last discussion of this. I remember it very well, and I remember being made nervous by some of the presentations about the manufacture of these devices and the possibility of less

thorough and complete standards being applied by companies.

But I think that with the guidelines that we discussed I feel very comfortable with the sort of parameters that were listed for a guidance document.

ACTING CHAIRPERSON McCAULEY: Are there any other comments from panel members?

Dr. Blumenstein.

DR. BLUMENSTEIN: Well, I feel more like a consumer rep. here than a statistician, but I guess I have two concerns. One is the system by which events are recorded, the data that was put up from I forget the name of that system.

DR. KRAUSE: Oh, the medical device recording, MDR?

DR. BLUMENSTEIN: Yes. It's very difficult for me to assess the meaning of the data because, number one, I don't have a denominator and, number two, I have no idea regarding the tendency to actually report events that do happen and to properly classify them.

Is there any way I can get a better description of that database and what requirements there are for it and any assessment about the possibility of missing a

significant number of events or anything like that? Can anybody speak to that?

DR. KRAUSE: That's actually a good question, and we anticipated last time that that question would get asked, and we had somebody from that group over here. It's the office, I think, of -- what is it? I can't remember the name of it. Surveillance and Biometrics actually, and there was somebody here that was ready to explain all of that, and since nobody asked last time, we didn't ask them to come this time and now of course, the question. So it's Murphy comes back and gets us once again.

DR. WITTEN: Well, I think that we can though say something about that system. So I'll say something to address your question, which is that system really isn't designed to look at incidence rates. It isn't designed to look at rates of events because there is certainly a question about what gets reported, and there's certainly, you know, a question about how many of these devices are used, and it's a large number.

I think what that system is primarily good for is for identifying new types of adverse events that people don't expect. So, in other words, in general I think if

somebody uses these products and they -- they may or may not work as well as the physician would like to see it work, but if the types of problems that he or she is having with the use of the products is within their experience of what, in general, they would expect with this product, in general, that wouldn't be something that that physician would tend to report.

So what we look for from that system is more identification of new types of things. So when Dr. Krause presented that list, it is more with an eye to looking at whether or not FDA has been able to identify the known risks with the device to make sure that the special controls that are proposed in the guidance document address all of the risks that were identified.

And I don't think that there was any intention to draw any conclusions about how frequently adverse events occur with these products. You wouldn't get that from the MDR system.

DR. BLUMENSTEIN: Yeah, and I didn't expect that either because I'm aware of the voluntary nature or more or less voluntary nature of this, but there's issues about attribution and whether, you know, a particular event that

might happen in a clinic somewhere, whether it actually gets correctly attributed, if there is that concept and so forth.

But really it's my second question that reflects back on this first question that's of more concern, and you raised the issue about whether the design of that system is to identify new things that are happening. So I gather the data is presented and you look at the particular things that have been reported, and you're not surprised by what's there, and you're pleased that there's not something that's new and unusual or like that.

My second question really has to do with, you know, what kinds of changes in technology over the next few years are going to lead to possible interactions with these devices, perhaps new drugs used during surgery or new techniques used during surgery or immediately post surgery that might interact with the absorbability or tendency for infections.

I don't know. I'm just making things up. I'm just a biostatistician, but are there any concerns in those directions and whether this system will be able to pick those up in sufficient time to react to them and so forth?

DR. WITTEN: Well, I think that that might be a

good question to ask your fellow panel members in terms of what kinds of things they might be concerned about, but I guess, you know, one question I would have would be as far as the reclassification whether that proposed reclassification -- whether or not, you know, Class III or Class II, we would be likely to get the type of data pre-market to address those kind of questions differently.

In other words, is there a difference for that kind of question between the two classifications?

I don't really know. I can imagine some situations where the MDR system wouldn't pick up some interaction or would pick up others just because, you know, a lot of times you have something happen where if the event is remote from the application site, it's probably less likely to be reported as an adverse event.

In other words, if there were something that happened systemically to the patient, I can't imagine what it would be that were related to an interaction, yes, people would be less likely to report it. If it was something that happened at the site, they'd probably be more likely to notice it, but it's really hard to address that except to say I'm not sure how that relates to the classification,

which is really a question of what kind of information, you know, we need. It relates to what kind of information we need about the product to put it on the market and regulate it on the market.

I'm not sure what difference the answer would be depending on the class of the product.

DR. BLUMENSTEIN: Yeah, I appreciate that the reclassification may not make any difference with respect to the interaction with other technologies and other techniques and so forth, but my issue is whether the system is sufficient to guard against those kinds of things because my sense is that the technologies are really changing quite rapidly in terms of things that are used during surgery and so forth, or at least that's what I see from my surgical friends.

And so that's the source of my question, is whether you feel like that there's sufficient mechanism in place to identify things that could be rather devastating, given the wide use of these devices.

DR. WITTEN: I don't think I have anything to add to what I have already said.

DR. KRAUSE: If I could add, the warning label

that's on products with thrombin and thrombin packaging itself was something that was picked up through the report, not the device reporting system, but reporting systems that showed that there was a very small subpopulation within the general population of people treated with thrombin who did develop these antibodies, and so the response to that was to put this warning on the labeling to warn, you know, the physician in charge to keep an eye out for these coagulopathies which could be induced by using thrombin.

And it's very rare, but it was picked up through some kind of a, you know, monitoring system. So that's an example of the system working.

ACTING CHAIRPERSON McCAULEY: Sorry. Are there any other comments?

DR. CHOTI: Could I make a comment, Robert?

This question I brought up last time perhaps to address to Dave is just still I think the definition or identification is still somewhat nebulous, and, Dave, you mentioned that there's kind of a reason to keep it vague, and I think that makes sense, but I'm still concerned that this idea of absorbable hemostatic agent intended to produce hemostasis is, as we move into the future with new products

and perhaps polymers, over the years it has been fairly consistent, subtle variations perhaps in these products, but recently now with the addition of thrombin and autologous platelets, there will be new devices, perhaps polymers or that are completely distinct.

Similarly, the vibrant sealants which have a different role, the Tissiel (phonetic) and HemoCure products and so forth may have a different role and don't fit into this category, but they are absorbable. They do provide hemostasis, and are there opportunities to get other devices or other products to fit into this classification based on this definition?

DR. KRAUSE: Do you want to answer that?

DR. WITTEN: Yeah. You know, if a new product with the same intended use in a new technology, if a manufacturer wants to submit an application for something that's got a new technology and the same intended use, then, you know, we would look at the product and look at the comparison to the product that's on the market and see whether the kinds of questions that we would, you know, ask about the differences in technology and what effect it has on performance could be addressed by data, and so, you know,

we have a flow chart algorithm to go through.

You know, what are the questions that this new technology raises and can it be addressed by data?

So that, as Dr. Krause said in his presentation, that data, you know, could be benchtop characterization for a newer technology that might well not be enough. That could include animal data, and if that isn't enough, then that can also include clinical data.

So we do see, you know, clinical studies as part of the potential spectrum of data that we would look at to evaluate what effect a difference in technology has on whether or not we can clear the product as substantially equivalent in performance to the products on the market.

ACTING CHAIRPERSON McCAULEY: Are there any other issues that the panel would like to discuss?

Dr. Leitch.

DR. LEITCH: Do the details of the guidelines address the pyrogenicity issues that were raised by Ms. O'Grady in terms of that level of detail?

DR. KRAUSE: Yes, they do.

MS. BROWN: I wanted to make one comment about pyrogenicity. I know that there's a level for neurosurgical

use, but I believe for medical devices there's a less stringent level for general surgical use, and so we probably should have the two levels represented.

DR. KRAUSE: Just to address Ms. Brown's comment, when the product is indicated for the general surgical use, which excludes neurological use and we go by the regular standard for medical devices; if, however, a company would like us to remove the neurological exclusion or add a neurological indication, then we would go to the pyrogenicity level, that is, you know, for neurological use, which is the .06.

ACTING CHAIRPERSON McCAULEY: Other issues, other questions?

(No response.)

ACTING CHAIRPERSON McCAULEY: At this point we will begin the focused discussion of the FDA questions. Can we have the questions placed on the screen for us?

The first question proposed to the panel states: please discuss the proposed reclassification of absorbable hemostatic agent and dressing. Please also discuss what descriptive information and intended use should be included in the classification identification.

We'll start with Dr. Lanzafame.

DR. LANZAFAME: Bear with me for a moment because I'm new to the panel, but from my vantage point as an end user and a researcher what I would like to see most is what the composition of the agent is, what its indications, contraindications and so on are included in the labeling.

The issue of pyrogenicity, what are the particular cautions? Is there cross-reactivity with other materials? And are there any special use applications? For example, insertion in minimally invasive strategies and so on may render the material difficult to use.

From the perspective of the quality control information, I believe that the information that is required and requested in at least the portions of the controls guidance document adequately cover those sections. So I won't discuss those further at this time.

ACTING CHAIRPERSON McCAULEY: Dr. Leitch.

DR. LEITCH: I think that the proposed reclassification is not unreasonable, but with the special controls guidance document. I think that answered a lot of the concerns I had with respect to ongoing safety for new

products that come into the field that resemble or are not exactly the same.

And then with respect to the intended use issues, I do think the differences at different sites need to be carefully explicated and that as new devices come up that there be the requirement to address those at the individual sites where specific problems have been recognized.

And it seems to me that most of the, you know, serious complications that are realized relate to some of these special sites, such as the neurologic sites and nerve compression. There's been little data to suggest there are significant antibody reactions.

So I think one of the biggest things is this application at different site, that that needs to be -- attention needs to be kept to that. I think the general surgical use doesn't seem to be as much an issue as some of the other special sites.

ACTING CHAIRPERSON McCAULEY: Dr. Choti.

DR. CHOTI: I agree that I think with these special controls as outlined I feel better about the reclassification to the Class II in this situation.

I think there are some variability in the special controls with each device. I think that as far as the intended use and descriptive material, I do think that Ann suggested that it needs to be site specific where it's applied and also with each different device there may be some variability based on how different it is and what some of the information, clinical or animal data, suggests as to what descriptive materials.

So that should be defined based on the material, but I think if that's clearly specified in the special controls, I think that it's reasonable to move ahead with that.

One question I do have regarding advice recommendation, how strict are some of these things in the special controls using the words "recommend" something or "advise" something?

DR. WITTEN: Is what you're asking what does the FDA with this special guide and how do we use it?

DR. CHOTI: Right.

DR. WITTEN: In terms of how we use it, the classification process and the guidance document address or list the kinds of risks that we see with these products, you

know, that we've experienced, and the guidance document gives a mechanism by which the sponsors can address those risks.

Now, they may choose not to follow exactly what's in the guidance. What they need to do is address the risks that are listed in the guidance.

So if there is some other way that they can do it, for example, sometimes we might list or suggest some specific kind of testing, and the sponsor may choose to do other testing. If we think that that testing also addresses the risk that's identified in the guidance document, then we would review that.

So it's an option. You could think of it as a list of risks that have to be addressed and a menu of options, you know, suggesting what we think is the best way to address or a way to address those risks.

And I think in general, you know, you have to look at these guidances and take them fairly seriously because, you know, it's a path. It's, you know, an algorithm to get to market for their product.

ACTING CHAIRPERSON McCAULEY: Dr. Blumenstein.

DR. BLUMENSTEIN: I have nothing to add.

ACTING CHAIRPERSON McCAULEY: Dr. Doyle.

DR. DOYLE: I think that most of the things that I have to say have been said, too. I think that the thing that struck me most as a consumer rep. is the fact that the guidelines, I think, have to be very clear that because of the differences in the materials of which these are made, if you've seen one, you've seen one. And I think it's very important that the guidelines are specific, and they do seem to be covering the various types of material, particularly, of course, those made from animal, tissues from animal origin.

ACTING CHAIRPERSON McCAULEY: Ms. Brown.

MS. BROWN: I agree that down classification in Class II with special controls would be appropriate. The quality system regulations are pretty good at controlling the manufacturing processes and assuring that as changes are made, design controls make sure that the products are reasonably safe and effective.

The biocompatibility standards for these products are pretty well understood and described.

I think Dr. Paulson covered very nicely that effectiveness can be looked at pretty carefully in animals,

in the animal models. That's understood pretty well.

With respect to intended use, I don't know if -- was this the time to talk about intended use or were we going to -- okay.

I think that out of the blocks the intended use should be the general intended use that was the kind described for Surgifoam with an exclusion for neurological ophthalmic and neurological, unless data is collected specifically to take those exclusions out.

I think all of the products that have come to market even under PMA have had those exclusions and have had to come up with some kind of specific data to address those, and I think that's still a good idea.

ACTING CHAIRPERSON McCAULEY: Dr. Miller.

MS. BROWN: And those are my comments.

ACTING CHAIRPERSON McCAULEY: Sorry.

DR. MILLER: I think that these products have been around for so long and there aren't a lot of ambiguities about how they work or what happens to them. I think that it's very reasonable to lower their level of regulation that they're subject to, and I think that the guidelines that have been suggested, I think they address

the concerns that have been talked about today and that we discussed last time, and it seems sensible to me.

ACTING CHAIRPERSON McCAULEY: Dr. LoCicero.

DR. LoCICERO: As the last person to sort of summarize, we're really talking about does it meet the definition of Class III anymore, and that is the devices for which insufficient information exist to determine there's safety and effectiveness, and there are few products around with this kind of history, and we do seem to have sufficient information at this point.

So I'm very comfortable with the down classification.

ACTING CHAIRPERSON McCAULEY: Dr. Witten, it appears that the panel is in favor of down classification of absorbable hemostatic agents and dressings to Class II with site specific requirements, particularly with respect to general intended use and neurosurgical use.

Does that satisfy your requirements for that question?

DR. WITTEN: Yes. Thank you.

ACTING CHAIRPERSON McCAULEY: The next question for the panel to discuss will be the risks. Please discuss

the risks to health for the absorbable hemostatic agent and dressings.

We will start with Dr. Leitch.

DR. LEITCH: Well, I've got into that a little bit before. I think that primarily where we're seeing them is then the application to enclose spaces with respect to neurologic injury.

And I guess what I would say, you know, a lot of times you might think that that would be a confined to a neurologic site surgery, but I think other sites should be aware that if they put it into a closed space even though they're not, quote, operating on the nerves, that they could experience complications relative to compression injury.

And so for me that seems to me to be the biggest concern that I have outside of some of these other issues of manufacturing performance which I think ought to be encompassed in the guidelines.

ACTING CHAIRPERSON McCAULEY: Dr. Choti.

DR. CHOTI: I think that really minimal risks to health that have been identified; I think they have been. The current products are well characterized with regard, I think, to health risks, which are minimal.

The issue, again, though is what is the future, and in other devices, as newer, combining with other products and so forth, I think we're going to just have to anticipate risks to health that we don't know about currently.

But I think certainly of the products we've seen the risks are minimal.

ACTING CHAIRPERSON McCAULEY: Dr. Blumenstein.

DR. BLUMENSTEIN: I have nothing to add.

ACTING CHAIRPERSON McCAULEY: Dr. Doyle.

DR. DOYLE: I think Dr. Choti said everything I wanted to say.

ACTING CHAIRPERSON McCAULEY: Ms. Brown.

MS. BROWN: I noticed in the Surgifoam package insert there's a statement about should not be used in instances of pumping arterial hemorrhage, and I was curious as to whether that was a precaution that was going to end up in most package inserts.

So I'll just open up. From my own experience with products like this, that pumping arterial hemorrhage challenges these devices quite a bit. So that might be an area that either there's a caution or there's data collected

to address that.

ACTING CHAIRPERSON McCAULEY: I think it has been previously stated that the use of these devices is primarily for hemostasis, obtaining hemostasis, which is not controlled by just the standard surgical methods.

Dr. Miller.

DR. MILLER: I don't think I have anything to add.

ACTING CHAIRPERSON McCAULEY: Dr. LoCicero.

DR. LoCICERO: In terms of the health risks, I think there really are two. One Dr. Leitch has outlined extremely well, and that is putting this into closed spaces, and that may be an issue of education that the manufacturers can take to the treating physician. It is a very low -- the rate is extremely low, and it's possible that many physicians have not experienced it, nor have they had the education about that issue.

And that would be something the manufacturers could bring to the physician.

The second is either failure of the device or failure to control hemorrhage for whatever reason. The intention is to control hemorrhage, and it's usually pretty

clear. It's either going to do it or it isn't, but there are situations where using the device covers up the hemorrhage, and one of the complications that's listed is hematoma as a result of continued bleeding, and it's unrecognized bleeding that might occur.

And this is, again, an issue of surveillance by the physician and recognizing that the product may or may not be able to control all hemorrhage.

ACTING CHAIRPERSON McCAULEY: Dr. Lanzafame.

DR. LANZAFAME: I think most of the comments have been well addressed. To echo what Dr. Choti said, really more from the perspective of newer agents that may be coming to the marketplace, while the previously identified risks look at inflammation, edema, wound dehiscence, generally speaking foreign body reaction and inflammation are only part of the wound healing cascade.

And as some of these strategies might be used in impaired hosts or oncologic applications, future products may need to look at their influence in some of these special states, which may not be generic.

ACTING CHAIRPERSON McCAULEY: Dr. Witten, it appears that several issues have come up relative to the

risk of health for absorbable hemostatic agents and dressings. Three that come to mind appear to be concerns of the use of these products to enclose spaces, also the risk of unrecognized hemorrhage, which is continuing, and a third appears to be related to the process of wound healing.

Are these issues enough to satisfy your concerns relative to Question No. 2?

DR. WITTEN: Yes. Thank you.

ACTING CHAIRPERSON McCAULEY: The third questions: are there any other risks to health for these devices that have not been identified?

We will start the panel discussion with Dr. Choti.

DR. CHOTI: Well, as we've just heard, one which I'm always concerned about not so much with this device, but the oncologic risk, the risk of cancer occurrence as this can be applied in areas of ablation, areas of cancer, and that's an endpoint we never see because you can never really track it easily. It applies to a variety of oncologic strategies.

Again, this hemostatic agent, it's not its main purpose, but it's a risk to health, that is, does it seed

cancer cells, does it, you know, this kind of thing. It's extremely hard to measure and we'll really never know that, but I think that's something that one always needs to keep in mind as a long-term health risk of a variety of types of devices.

ACTING CHAIRPERSON McCAULEY: Dr. Blumenstein?

DR. BLUMENSTEIN: I have nothing to add.

ACTING CHAIRPERSON McCAULEY: Dr. Doyle.

DR. DOYLE: I guess the answer to that is I hope there aren't any that we don't know, but there may be. I think, with new things coming along, we have to be constantly vigilant.

ACTING CHAIRPERSON McCAULEY: Ms. Brown.

MS. BROWN: I have nothing to add.

ACTING CHAIRPERSON McCAULEY: Dr. Miller.

DR. MILLER: I have nothing to add, but I just have a question. We've discussed new devices. I just want to be clear in my own mind. If something totally new comes up that falls into this category, say, some synthetic polymer that is unlike anything that's ever been created that's designed to do what these devices are designed to do, that would no longer be substantially equivalent; isn't that

correct? And it would have to be treated differently than these, you know, collagen devices and that sort of thing?

DR. WITTEN: It depends. What we do is we look at the devices on the market, and we look at the new device proposed for market and see whether the new device raises any new types of questions that we wouldn't ask about the old devices.

In other words, you know, if the questions that we would ask about a new proposed device are just, you know, does it control the bleeding, the questions that we relate to the risks that we've just discussed, then what we would then do is see whether we could address those questions by data.

Now, if it raised some new types of questions, and I'm not sure what those would be because we haven't seen those products yet, but I'm sure that, you know, you could imagine something sufficiently novel that, you know, there are some new types of questions about it.

Then we would. It wouldn't fall into this. But the answer is, yes, it depends. So the answer is, yes, if there's a product made of a new material that is not fit exactly in this descriptive classification, what we would do

would be to evaluate it against the existing products to see whether, you know, the kinds of questions that we would ask about that kind of product are similar to the kinds of questions we ask about the existing product or it's sufficiently novel to raise new types of questions.

So I guess that's clear, I hope.

ACTING CHAIRPERSON McCAULEY: Any other questions, Dr. Miller?

DR. MILLER: I don't think so.

ACTING CHAIRPERSON McCAULEY: Dr. LoCicero?

DR. LoCICERO: Excuse me. I'd like to echo Dr. Doyle's comments. The eye does not see what the mind does not know. So we need to be very open and vigilant about potential new complications.

ACTING CHAIRPERSON McCAULEY: Dr. Lanzafame.

DR. LANZAFAME: I have nothing to add.

ACTING CHAIRPERSON McCAULEY: Dr. Leitch.

DR. LEITCH: I have nothing to add. Thanks you.

ACTING CHAIRPERSON McCAULEY: Relative to the third question, Dr. Witten, it appears that outside of the development of new devices which may interact positively or negatively with the hemostatic agents, there are no

significant health concerns that can be identified at this time.

Does that satisfy your requirements for that question?

DR. WITTEN: Yes. Thank you.

ACTING CHAIRPERSON McCAULEY: The next item on the agenda will be to reclassify questionnaires and votes. We will complete the classification questionnaire and the supplemental data sheet.

Dr. Gatling from the Office of Device Evaluation will assist us as we go along.

After panel discussion of each question, I will note your answer for each blank on the data sheet, and Dr. Gatling will record it on the overhead for us. We will vote on the completed questionnaire and supplemental work sheet. It will become the panel's recommendation to the FDA.

Are there any questions before we proceed?

(No response.)

ACTING CHAIRPERSON McCAULEY: Let's begin. Dr. Gatling, will you proceed with the questionnaire, please?

MR. GATLING: Yes. My name is Bob Gatling. I'm the Director of the Program Operations Staff in the Office

of Device Evaluation.

Normally we would have a presentation to talk about classification and reclassification and how that all fits together, but given where you are in your deliberations, Dr. Witten and Dr. Krause, do you want to just proceed right to the questionnaire and the supplemental data sheet?

DR. WITTEN: No, I don't think so.

MR. GATLING: Do you want me to go over a few of the slides then?

I'm just going to highlight a few of the slides that I have in my presentation here. Normally Marjorie Shulman of the 510(k) staff presents this presentation. These are her slides, and it's geared toward classification of devices that were on the market before 1976, which is not applicable today.

It's also for reclassification, which is applicable today.

These are the kinds of things that she would normally go through. A little background material. The medical device amendments of 1976 established a classification procedure for devices. It set up the 33

classes, Class I, II and III, and at the time that the medical device amendments were passed, it was charged to FDA to classify every product, every medical device that was on the market beginning in 1976. So we had a big task in those early days.

The law also provided for reclassification based on new information of those devices, which is more applicable today.

These are some other laws that are listed that have been passed in 1990, FDAMA in 1997, and a more recent one, medical device user fee of 2002.

Pre-amendments versus post amendments information. Just to give you a little bit is those that were before 1976 were classified. This particular product was a transitional device as Dr. Krause mentioned earlier and automatically placed in Class III. You did not have to go through a classification process.

To keep moving through these things, so the reclassification of the pre-amendments, and we may reclassify pre-amendments devices in a procedure that parallels the initial classification, and that's going to be the questionnaire in the supplemental data sheet plus the

panel deliberation, and it's based on new information.

And now that we have kind of come to this point with these products being on the market since the 1940s, I think there's a lot of information to base this information on.

Post amendment devices, not applicable for this one. Again, another slide.

Class I. It has been reiterated in some of the earlier presentations today what a Class I device is, and these are where general controls are sufficient to provide that reasonable assurance of safety and effectiveness. This is the lowest class of regulatory control.

And these general controls include prohibition against adulteration and misbranding, the pre-market notification 510(k) requirements, banned devices, good manufacturing practices, registration and listing, record keeping and repair, replacement, and refund, general control.

Class II devices are ones where the general controls in Class I are not sufficient to control the risk to health, and so it provides for special controls which adds onto the general controls to control these different

risks associated with it.

And with those two, general controls and special controls, the risks to health are sufficiently addressed, and these special controls can include performance standards of the various types, post market surveillance studies, discretionary studies if we want to do that, patient registries, and traceability and development dissemination of guidances, which is the main point, I think, that you've been talking about today.

And you can get very detailed into that guidance document of the kind of information that companies need to present to FDA in their marketing application, and you are very detailed in yours, including design controls.

Recommendations could include special labeling. I think you have some of those things in tracked devices.

Class III where this device currently exists is where there's insufficient information to determine the safety and effectiveness of the device. I think at the time in 1976, that since they were undergoing review as new drugs, that the agency felt that those should move right into Class III and stay in that category until reclassified. So I think we're at a different point today than we were

back at that time.

And the new information that we should be considering is should be valid scientific evidence, and these are the kinds of information that's considered valid scientific evidence in clinical trials.

A recommendation for the initial classification and a reclassification of this panel meeting is what we really need, and we're going to be using some tools today, this questionnaire and the supplemental data sheet to capture the information that's needed as part of the reclassification.

And these are just some detailed things that we will actually go through with those particular ones, and at this point, unless there are any particular questions, I would like to go ahead and move to the questionnaire and the supplemental data sheet.

And what I recommend we do is we go through. Some of these are like identify the risk to health. You can just refer back to the discussions, what's been provided in your information that you received prior to the panel, and any additional risks that you've identified as part of your discussions. We don't have to relist that. We can capture

that from the record.

Okay. I handed out the supplemental data sheet and the questionnaire. We'll go through the questionnaire first.

Okay. So I'm just going to kind of skip through some of these we note. Go to Question 1. Is the device life sustaining or life supporting?

I'm assuming no. Yes? I need to answer the questions. I'm sorry.

ACTING CHAIRPERSON McCAULEY: All those who voted yes on the first question raise your hand.

(Show of hands.)

ACTING CHAIRPERSON McCAULEY: Those who vote no?

(Show of hands.)

ACTING CHAIRPERSON McCAULEY: Could we get a recount?

Those who voted yes?

DR. LEITCH: Could I ask a question?

ACTING CHAIRPERSON McCAULEY: Sure.

DR. LEITCH: Are there some specific definitions of those two things, life sustaining and life supporting?

DR. KRAUSE: I'll try to address that, and, Dr.

Witten, since it's your area, you might want to add onto that.

A life sustaining and a life supporting device is where if there's a failure to perform as it should could lead to death or serious injury. So I think you have to look at the application, what these things are used for, to maybe answer that, and sometimes maybe it's yes and sometimes no.

ACTING CHAIRPERSON McCAULEY: Okay. Are there any other questions before we take a vote on this question?

Those panel members who voted yes?

DR. MILLER: Could I ask one question before we vote?

ACTING CHAIRPERSON McCAULEY: We'll get through this.

DR. MILLER: I mean, I can envision a situation where it would be life threatening if this device failed. So if there is a situation where that's true, does that make it a life sustaining and life threatening device?

But in many situations it fails and it's not life threatening, it's just a problem that you can fix. So which wins in each classification?

DR. KRAUSE: Yeah, I think it's the general use of the device. It's not, you know, if there's one out of a million situations or something like that. It's the general use of the device, if the general way the device is used isn't life sustaining or life supporting.

DR. MILLER: Okay. Thank you.

ACTING CHAIRPERSON McCAULEY: Are there other questions relative to this issue before we vote?

DR. BLUMENSTEIN: Yes. So the phrase "device failure" was used. Now, device failure could be the misapplication of the device by the person like the surgeon or it could be that the manufacturer -- there's a lot of this device that is incorrect.

Which applies here? I mean, if there's a bad lot that causes infections, that causes death, then it seems to me that that's definitely life threatening, but does that apply to this question?

DR. KRAUSE: I don't think so because the way the question is worded is or the intent is if the device is made correctly according to specifications and used in the way it's labeled, does it function the way it's supposed to function? Is it life sustaining or is it not?

So it's not looking for the exceptions to the rule. It's basically a question for the general use of the device, the general manufacture of the device if everything is done according to specifications and the indications for use.

ACTING CHAIRPERSON McCAULEY: Other issues?

(No response.)

ACTING CHAIRPERSON McCAULEY: Once again we'll try this question again, Dr. Gatling.

MR. GATLING: Okay.

ACTING CHAIRPERSON McCAULEY: Those who vote yes to Question 1.

(Show of hands.)

ACTING CHAIRPERSON McCAULEY: Those who vote no?

(Show of hands.)

MR. GATLING: Okay. Question 2, is the device for use which is of substantial importance in preventing impairment of human health?

ACTING CHAIRPERSON McCAULEY: Those who vote yes?

(Show of hands.)

ACTING CHAIRPERSON McCAULEY: Those who vote no?

(Show of hands.)

MR. GATLING: Okay. Thank you.

Question 3, does the device present a potential unreasonable risk of illness or injury?

ACTING CHAIRPERSON McCAULEY: Yes?

(Show of hands.)

ACTING CHAIRPERSON McCAULEY: No?

(Show of hands.)

DR. KRAUSE: Oh, by the way, everybody should be filling out their particular form as to how they're voting so that we can collect them in the end, except for the non-voting members.

ACTING CHAIRPERSON McCAULEY: Question No. 4.

MR. GATLING: Okay, Did you answer yes to any of the above? Yes, you did. Go to six.

Is there sufficient information to establish special controls in addition to general controls to provide reasonable assurance of safety and effectiveness?

ACTING CHAIRPERSON McCAULEY: Those who vote yes?

(Show of hands.)

ACTING CHAIRPERSON McCAULEY: Those who vote no?

(Show of hands.)

MR. GATLING: Okay. Thank you.

Okay. Question 7, if there's sufficient information to establish special controls to provide reasonable assurance of the safety and effectiveness identified below, the special controls needed to provide such reasonable assurance for Class II, and this includes listed on the form guidance documents, performance standards, device tracking, testing guidelines, and then other.

And if the information that's provided in the pre-panel information and your discussion is sufficient in your mind, then you can consider that.

ACTING CHAIRPERSON McCAULEY: Is there any discussion of this question before we proceed?

DR. LEITCH: Could I ask a question about Number 5? Did the panel vote yes to Number 5? Did I get that correctly?

Because if yes, that's a Class I.

DR. KRAUSE: No. What happened was when we voted on Items 1, 2, and 3, one of those was yes. So we skipped to six.

DR. LEITCH: Okay.

DR. KRAUSE: Okay?

DR. LEITCH: Okay.

DR. KRAUSE: So there was no reason to vote on five.

DR. LEITCH: Okay.

ACTING CHAIRPERSON McCAULEY: Will the guidance document provide sufficient information for special controls related to absorbable hemostatic agents?

How many vote that a guidance document is sufficient?

DR. MILLER: Can we -- may I ask a question? Can we just say in this whole section to refer to our discussion that we had and have that be sufficient for all of these?

ACTING CHAIRPERSON McCAULEY: Dr. Witten, is that reasonable?

DR. WITTEN: Yes.

DR. BLUMENSTEIN: I just had one comment. I heard several people mention education as being important here, and what I can't recall just offhand is was that covered in the guidance document.

DR. KRAUSE: Education is specifically not covered in the guidance document, but if you look at the very back of your packet of information, there's the labeling for the product Surgifoam, and you can see that the labeling is very detailed, and it talks about, you know, when you apply the device once hemostasis is achieved, that you should remove as much of the device as possible.

So that's kind of stuff that has been learned by education over the years of using these devices, and we would insist on basically that kind of labeling for these devices. It's very informational. It includes all of the precautions, all of the warnings, all of the, you know, contraindications and things like that that we have discussed.

DR. CHOTI: So the discussion, your presentation, Dr. Krause, is a guidance document. It's not a performance standard, tracking or any of these others. It's only a guidance document; is that right?

DR. KRAUSE: Right, right.

ACTING CHAIRPERSON McCAULEY: Question?

DR. CHOTI: So perhaps we should vote on whether these other -- so the guidance document is perhaps as

discussed. The question is whether these other controls should also be included for any of them.

ACTING CHAIRPERSON McCAULEY: Dr. Witten, can you clarify this for us?

DR. WITTEN: Well, we're asking you to identify the special controls needed to provide such a reasonable assurance, and what we have proposed in our discussion is that we have a guidance document that we think covers, you know, the special controls that we think is needed to provide reasonable assurance of safety and effectiveness.

If there are any other things that you think, you know, are also needed, then you certainly are free as a panel to suggest what those are, but our suggestion was and is the guidance document.

But I'd be glad to answer any questions about the other things listed on this list if you'd like.

ACTING CHAIRPERSON McCAULEY: Dr. Krause, do you have any comments to add?

DR. KRAUSE: No, I agree with Dr. Witten.

ACTING CHAIRPERSON McCAULEY: Dr. Blumenstein.

DR. BLUMENSTEIN: Well, I'd just like to ask what device tracking is.

DR. WITTEN: Yes. Device tracking means that the device can be tracked to the patient so that every time that a device is used, the manufacturer is informed of who it was used in and is able to locate that patient so in case that later something turns out with the device that they want to contact that patient, they can get in touch with them.

So I'm not actually -- to be honest, there are not a lot of tracked devices. I'm not sure exactly what they are, but, for example, if you had an implantable heart device that if it failed the patient would be, you know, at risk of death on failure and the sponsor discovered some mechanical problem with their device and wanted to be able to get in touch with those patients to let them and their physicians know, it would enable them to know in whom that product was used.

DR. BLUMENSTEIN: So this is not like putting a cell phone in there so that it can be tracked and the patient can be located at any moment then, right?

DR. WITTEN: No, but it is to be able to specifically be able to identify those patients.

DR. BLUMENSTEIN: Right. No, I understand now.

Thank you.

ACTING CHAIRPERSON McCAULEY: Are there any other questions?

Dr. Leitch.

DR. LEITCH: Well, with respect to the education issue, you know, we're referred to the Surgifoam insert, and the issue I raised of, you know, these other sites, but then, for example, for general surgical use where you might be using it in a closed space or you might have some extremity surgery and you're using it on a tendon, but you're not repairing a tendon, but it's in the vicinity of a tendon or if you're running down this list quickly to look at the contraindications, you might not realize that particular issue because it's kind of subsumed under sites that the person wouldn't be operating on, and so I think that's what, you know, we're mentioning in education, that some of these things may be unknown to people who don't operate in those sites, but yet they could be pertinent to a site where they are operating even though it's not a neurologic procedure.

ACTING CHAIRPERSON McCAULEY: Any comments from anyone else?

(No response.)

ACTING CHAIRPERSON McCAULEY: Would it be prudent to ask whether or not, as Dr. Choti suggested, that the panel members can vote multiple times on the same question because there are different issues that are addressed in each one of these items?

DR. KRAUSE: Well, I think anyone can suggest any of those methods for the special control, and you don't only have to have one. You can certainly have more than one, and if there's one that's not listed there that you think should be considered as a special control for that type of device, you can add it under "other."

ACTING CHAIRPERSON McCAULEY: Do any of the panel members feel that performance standards need to be part of the controls?

(No response.)

ACTING CHAIRPERSON McCAULEY: Device tracking, is that an issue for special controls?

(No response.)

ACTING CHAIRPERSON McCAULEY: Testing guidelines, are those issues for special controls?

(No response.)

ACTING CHAIRPERSON McCAULEY: There's no comment from the panel. So it appears that none of the three mentioned items are required special control issues.

Does the panel have any other special control issues that need to be addressed under "other"?

(No response.)

ACTING CHAIRPERSON McCAULEY: Then we can move on to the next question.

MR. GATLING: Okay. Question No. 8 has to do with performance standards. Since you are not recommending a performance standard, it's not applicable. The same thing with Number 9, not applicable.

Number 10, for a device recommended for reclassification to Class III, identify. That's not applicable.

Okay. The next page. Identify the needed restrictions only upon the written authorization of a practitioner licensed by law to administer or use the device, used by persons with specific training or experience in its use, used only in certain facilities or other.

ACTING CHAIRPERSON McCAULEY: Are there any issues relative to Question No. 11?

(No response.)

ACTING CHAIRPERSON McCAULEY: No.

MR. GATLING: Well, I think one of the main things there, should it be a prescription device.

ACTING CHAIRPERSON McCAULEY: I'm sorry?

MR. GATLING: Should it be a prescription device? That would be a needed restriction.

ACTING CHAIRPERSON McCAULEY: Any discussion from panel members?

DR. MILLER: When you say prescription, I mean, you don't write a prescription for something you use during a surgery. But I think a person needs to be trained to use it, of course, and needs to be licensed to use it. I mean, a physician, a surgeon needs to have the training. I don't think he needs to have a special facility. Any surgical situation would be appropriate.

Would you check off those two boxes?

MR. GATLING: Okay. Generally for this particular question what we're looking for is whether it should be restricted to prescription use versus over the counter. That's where the distinction comes in. And it's prescription even though it's used in surgery. There's a

presumed prescription at that point.

The others having to do with training is one where you feel that before a physician can actually use the device, some sort of a training program -- he or she needs to go through that and actually use that. That's where these restrictions come in.

DR. MILLER: Like specifically training on that device or --

MR. GATLING: Yes, correct.

DR. MILLER: -- surgical training in which the device is a part of what you're trained to use?

MR. GATLING: That's correct. It's very specific to this device, not general medical or specialty training.

DR. WITTEN: Let me just clarify. When you use something in surgery, even though you're not writing a prescription for it, I mean, you know, it's like asking for a medication during surgery. It's considered a prescription because, you know, you've got a nurse. You've asked for it and you're administering it, that kind of thing.

DR. MILLER: I understand.

DR. LoCICERO: I might also add that this is a

ubiquitous use product, and so during our training we use it ubiquitously. So I'm not sure that we need special training.

ACTING CHAIRPERSON McCAULEY: Other comments from the panel members?

MS. BROWN: I think with regard to the training the current products under PMA don't require training to my knowledge. So to start adding it at this point probably doesn't make sense.

ACTING CHAIRPERSON McCAULEY: I agree. I think that as Dr. LoCicero mentioned, this product is used ubiquitously, and if we're down regulating it to a lower class, it seems we're going backwards to require training.

DR. MILLER: I guess I considered surgery, you know, training. A surgeon should put it in.

(Laughter.)

ACTING CHAIRPERSON McCAULEY: Are there any other comments from panel members?

Dr. Leitch.

DR. LEITCH: Well, the issue of prescription versus not, I mean, are you asking us to make a discrimination of, you know, could this be used by the lay

public as a Bandaid or something like that? Is that --

MR. GATLING: That's what this question would address, and it would be available at your local pharmacy for anybody to pick up on the shelf and take home and use.

DR. KRAUSE: Yeah, I think what it's talking about is would it be labeled with the federal law requires, you know, that this be used only by a licensed practitioner, that type of labeling, which would ordinarily be considered the prescription labeling as opposed to over-the-counter labeling where anybody could apply it.

ACTING CHAIRPERSON McCAULEY: Dr. LoCicero.

DR. LoCICERO: As we went through our discussion this morning, was it not the FDA's recommendation that this be restricted to use by physician?

DR. WITTEN: By a practitioner.

DR. LoCICERO: Practitioner. Sorry.

ACTING CHAIRPERSON McCAULEY: Can we proceed to a vote on this question?

Just on the first item which states that only upon written and oral authorization of a practitioner licensed by law to administer use of this device, those who say yes.

(Show of hands.)

ACTING CHAIRPERSON McCAULEY: The next question: use only by persons with specific training or experience in its use. Those who vote use?

(No response.)

ACTING CHAIRPERSON McCAULEY: Those who vote no?

(Show of hands.)

ACTING CHAIRPERSON McCAULEY: We have a unanimous vote of yes for the first question and a unanimous vote of no for the second question.

The third question states whether or not this product should be used only in certain facilities. Any discussion before we vote?

(No response.)

ACTING CHAIRPERSON McCAULEY: Those who vote yes?

(No response.)

ACTING CHAIRPERSON McCAULEY: Those who vote no?

(Show of hands.)

ACTING CHAIRPERSON McCAULEY: That again is a unanimous no.

Dr. Gatling, does that complete the questionnaire?

MR. GATLING: Thank you very much. That's great.

Now we can move to the next document, the supplemental data sheet. Generic type device is the name of the product as we're discussing today in this advisory panel. Device and implant, and that's defined as in the body for greater than 30 days.

Dr. Witten, how is this currently listed? Is it listed as an implant?

DR. KRAUSE: It's absorbable, and the time to full absorption for some of these is close to 30 days. So it's kind of --

MR. GATLING: I would say probably no then.

DR. KRAUSE: What's that?

MR. GATLING: I would say no, it's not an implant given that.

DR. KRAUSE: Okay.

MR. GATLING: It's less than 30 days.

Indications for use. You had an identification. Is that sufficient or do you want to have anything in

addition to what was up there?

ACTING CHAIRPERSON McCAULEY: Any comments from the panel?

DR. KRAUSE: I think Ms. Brown had a suggestion earlier which was dealing with here's the indication.

MS. BROWN: Well, to use either the indication that's in Surgifoam's package insert, which is at the back of the package. Also I know that other companies that have gone before have had intended uses that didn't have the language dealing with capillary, venous, and arteriolar bleeding.

But I do think the indicated use statement should, unless there's specific data to address it, have neurological, ophthalmic and neurological exclusions just because that's historically what these agents have had.

DR. KRAUSE: So the panel can vote to use the indication as stated in the Surgifoam labeling or any variation. So if you think it should be different than that, you can certainly say that or you can just agree that that's an appropriate indication.

It's in Tab 7, and that's the general indication that these devices are approved. The wording may be

slightly different, but that's the general idea, is that these devices are used in general surgical applications with those exclusions when conventional means fail.

And the conventional means are ligature, cautery, pressure, and those types of things, or it's impractical which means if a surgeon would like to -- needs to stop bleeding, but it's in a place where he can't get a cauterizing iron or he can't get a suture. Then you would want to use one of these devices, and that's basically what the intent is of that indications for use statement.

MR. GATLING: Also, I'd like a clarification that you had a device identification that's currently in the CFR. Are you comfortable with that wording, given the reclassification of that? re there any changes needed to that?

DR. CHOTI: Just for clarification, that was the statement that this was used for stopping bleeding and that is absorbs.

MR. GATLING: Right.

DR. CHOTI: And that's the general definition.

MR. GATLING: Are there any changes to that that you would recommend?

DR. CHOTI: No.

MR. GATLING: Okay. Identification of --

ACTING CHAIRPERSON McCAULEY: Before we move on --

MR. GATLING: Oh, sorry.

ACTING CHAIRPERSON McCAULEY: -- we need to take a vote as to whether that is an acceptable indication for device labeling.

DR. LEITCH: Are we talking about identification or indication?

ACTING CHAIRPERSON McCAULEY: Identification or indication. I'm sorry.

MS. LEITCH: Because there's identification, which is --

ACTING CHAIRPERSON McCAULEY: That's next.

MS. LEITCH: -- absorbable -- that's next?

MR. GATLING: No, this actually really should capture the identification that's going to be put into the CFR, and that's why I asked that, to clarify your recommendation on the current --

ACTING CHAIRPERSON McCAULEY: So that question basically is not on the questionnaire, but we are voting now

for the identification.

MR. GATLING: Right, and also your indication statement. That's a good thing to have for the labeling part of it.

DR. LEITCH: So if I understand the identification is absorbable hemostatic agent, surgical, is an absorbable device intended to produce hemostasis by accelerating the clotting process of blood during surgical procedures. That's identification?

MR. GATLING: That's correct.

DR. LEITCH: Okay. That's different than indication, which is the intended use.

ACTING CHAIRPERSON McCAULEY: Well, we're saying that that's identification, which Mr. Gatling is asking, which is not part of the questionnaire.

DR. KRAUSE: Do we have a question on that, Bob?

MR. GATLING: No, actually this data sheet is both the initial classification and for reclassification, and it's a dual use document.

DR. KRAUSE: Okay. So we're saying that Number 4 is both asking about the indication for use and the product identification?

MR. GATLING: Correct. During initial classification usually what you're working with is the current indication, which we then develop into an identification for regulatory purposes. So this document tries to capture that.

And I want to clarify that the reclassification of this generic type that is proposed today, is there any changes to the current identification that we've already developed in the original development of the CFR?

ACTING CHAIRPERSON McCAULEY: I think we're going to review the CFR identification of hemostatic agents and dressings and see if that's acceptable to panel members.

DR. KRAUSE: This is the identification, product identification that we're proposing, which is I think identical to what it is now.

DR. LEITCH: It doesn't have "dressing" in it, right?

DR. KRAUSE: Right. We took the word "dressing" out. We just wanted to say absorbable hemostatic agent, surgical because the fact is that there are certain sound dressings that have hemostatic properties, and those are not in this classification. So we thought the name was

confusing. So we just thought it would be appropriate to change it to surgical.

DR. CHOTI: I still have a little bit of a problem with this identification in its vagueness. You know, why doesn't bone wax or fibrin sealants fit that classification in some way?

So it's a vague definition that just includes absorbable clotting process, hemostasis, but I just can't think of a better way to phrase a definition or identification.

MR. GATLING: When we developed the identification, what we wanted to try to do is capture the broad category of the devices so that things would fit in there naturally. If you make it so restrictive that when new products are coming in you can't use that category, they end up falling out into a different regulatory category. So that was the reason that the identifications were kind of broad even though when we actually get the files and we're reviewing those they may fit in there and the category kind of expands and gets narrow depending on the particular product.

So we try to keep it big, but we can use the

very specific things that we need to be.

DR. WITTEN: Also, I'll just say that fibrin sealant is a biologic project, and when we're reviewing these if it's something like bone wax where the indications for use wouldn't fit in with the predicate, then it doesn't fit in with this category.

In other words, this is an identification of the category, but then when you get an application, you review it in comparison with the other products that are in that category, and in comparison with their labeling, their intended use and what they're made of.

So it doesn't mean that somebody would just come with a product that could fit into what you term, you know, vague or we'd call it broad category, and that means they get on the market. They need to make a case in comparison with a specific product that already exists in that category.

DR. KRAUSE: Right, and also, bone wax doesn't meet that definition because it does not accelerate clotting. It merely acts as a tamponade. It just blocks bleeding. It doesn't really induce hemostasis, which these products do.

DR. CHOTI: It's somewhat semantics. I mean, a hemoclip, an absorbable hemoclip, you know, yes, that just blocks the vessel, but ultimately it does inhibit the clotting cascade to some degree.

Again, it's semantics. I don't know of a better definition. I agree there are advantages to keeping it broad, but it's a little bit problematic.

ACTING CHAIRPERSON McCAULEY: Is the identification of hemostatic agents as outlined by Dr. Krause in this slide, is that acceptable to the panel?

(Show of hands.)

ACTING CHAIRPERSON McCAULEY: Yes. Okay. Now we can move on to indications.

MR. GATLING: Thank you.

One clarification. What happened to dressings? Because I know this is going to come up as we proceed with a reclassification. Are you including the dressings in this? No? Okay.

Okay. Question 5 is the identification of any risk to health presented by the device, and I think you all have a nice list if you want to just refer back to that one.

DR. KRAUSE: Oh, we're just going to have a vote

on the indication now.

MR. GATLING: Oh, sorry.

ACTING CHAIRPERSON McCAULEY: Could we have a recap of indications for use in the device labeling?

DR. KRAUSE: Let me read an indication. Absorbable hemostatic agents are used, dry or saturated, with sterile sodium chloride -- and that part doesn't need to be in there -- as indicated for surgical procedures, except urologic, ophthalmologic, and neurologic for hemostasis when control of bleeding by pressure ligature or other conventional procedures is ineffective or impractical.

ACTING CHAIRPERSON McCAULEY: Can we have a vote on indications or at first is there any discussion about the indications for this product?

DR. CHOTI: Just one question regarding urologic, ophthalmologic and neurologic.

ACTING CHAIRPERSON McCAULEY: Yes.

DR. CHOTI: Is there evidence to suggest it's -- I mean, should we have discussion regarding whether that should be excluded?

ACTING CHAIRPERSON McCAULEY: Dr. LoCicero?

DR. LoCICERO: I think from all of our

discussion this morning that it's included with specific guidelines. We spoke specifically about pyrogenicity and the level that is required for neurologic. So we actually have included it, and so my suggestion is that we leave that piece out of the indications, and our guideline, our controls are going to take care of that issue.

ACTING CHAIRPERSON McCAULEY: Any other discussion?

DR. WITTEN: So I missed that. So is the intended use going to not have exclusions or have exclusions? I don't understand what the intent is right now.

DR. LoCICERO: I would suggest that we leave out that phrase because, in fact, it is indicated in those three areas. It is used in those areas. So it doesn't make sense to exclude that from the indications.

MS. LEITCH: And it would be the manufacturer's responsibility to say the circumstances in which, you know, they have data to say it shouldn't be used, and this particular manufacturer has indicated these sites, but I don't think everyone who would do a hemostatic agent would think it wasn't useful in the other site.

So I think that, you know, some sites have raised concern, and that any new product would have to address concerns in those sites. But I think to put the identifier as indication to exclude sites when a new product might be okay for those sites wouldn't be appropriate, but yet --

ACTING CHAIRPERSON McCAULEY: But these are all labeling issues.

Dr. Lanzafame.

DR. LANZAFAME: Yes. Having dealt with this before, just a reality check. Am I correct in presuming that each intended use and indication for use, which indeed are labeling issues, the more specific they become across devices and products, the more specific the controls on the part of the manufacturer in terms of providing data to actually support those indications?

DR. WITTEN: Well, I think that's generally the case. The situation is we don't actually need a vote on this. I think these recommendations for labeling, and you know, we'll take what you said into account while we look at the labeling guidance, but what we would do is exactly, you know, like what you've suggested, which is for a specific

product look at what the predicate device labeling is, look at that device's labeling and see whether, you know, if there are differences we need additional information to support those differences.

So I think, you know, we've had some discussion about that, and I think we can move on sine we don't need that for the supplemental data sheet. We don't need a vote on that; is that right?

MR. GATLING: That's correct. This is a recommendation of how the wording should be.

DR. WITTEN: Right. So I think we can go on to talk about the identification of risks, and that's what we need a vote on from you all, I mean, unless there's some additional comments. But I think as was just stated, this would be something we would look at for the labeling of that specific product because, as you just said, when we reviewed that specific product.

ACTING CHAIRPERSON McCAULEY: So we're on identification of any risk to health presented by the device, correct?

DR. WITTEN: Yeah, and you can refer back to your prior discussion.

ACTING CHAIRPERSON McCAULEY: Yes, we can actually refer that back to one of the questions that we answered in the earlier FDA session. Is that acceptable?

DR. WITTEN: It's acceptable to us if it's acceptable to the panel.

ACTING CHAIRPERSON McCAULEY: Is that acceptable to the panel?

(No response.)

ACTING CHAIRPERSON McCAULEY: Let's move on to the next question.

MR. GATLING: Okay. Recommended advisory committee's classification and priorities. So classification, Class I, II or III.

ACTING CHAIRPERSON McCAULEY: Does everyone agree with Class II? Yes or no? Those who vote yes?

(Show of hands.)

ACTING CHAIRPERSON McCAULEY: The vote is unanimous for Class II, device reclassification.

MR. GATLING: There's another question here regarding priority, and it has to do with performance standards, and since there's no performance standard.

It's not an implant or life supporting. So we

skip Number 7.

Number 8, a summary of information including clinical experience or judgment upon which classification recommendation is based, and you have a lot of information. You can refer to the information that you have in your clinical experience if you want.

ACTING CHAIRPERSON McCAULEY: We can also, if it's acceptable to the panel, we can also refer this question to the earlier discussions with the FDA, if that's acceptable. Okay.

MR. GATLING: Okay. Identification of any needed restrictions on the use of the device, special labeling banning prescription use. This is where the prescription thing comes in again and any special labeling which you may have which you could refer back to the guidance document as part of your special controls. There's a labeling section in there, I believe.

ACTING CHAIRPERSON McCAULEY: Does the panel object to referring back to the guidance document for labeling issues?

(No response.)

ACTING CHAIRPERSON McCAULEY: No? Then we can

move on to the next question.

DR. WITTEN: Move on to 11.

MR. GATLING: Okay. If the device is recommended for Class II, recommend whether FDA should exempt it from pre-market notification. In other words, we would not see a pre-market submission for these types of devices if you vote to exempt it.

ACTING CHAIRPERSON McCAULEY: Any discussion from the panel?

DR. BLUMENSTEIN: My form says Class I.

DR. WITTEN: We skipped Question 10. We're moving on to Question 11.

DR. BLUMENSTEIN: Oh.

DR. CHOTI: Would you just clarify something for me? So if it's this Class II, it's still possible to have a -- is this where we're deciding whether one can still have a PMA in this class?

DR. WITTEN: No. What Question 11 says is do you think that the manufacturer should submit an application to us prior to going to market, 510(k) Class II application, or do you think they can go to market and just, you know, follow the guidance and the special controls without

submitting an application?

So exempt means no application and not exempt means we review it before market.

Yes? Oh, sorry. Yes.

DR. BLUMENSTEIN: My issue here would be the surveillance. If they just go to market without notification, does that mean they're not under surveillance?

DR. WITTEN: Well, if they go to market without notification, that means we don't review the information regarding their product prior to going to market, which in general for these, you know, I don't know of any other exempt devices that are -- I mean, I can't think of any.

We do have some Class II exempt devices. I'm sorry I can't come up with some examples, but exempt means we don't review the information regarding the product, but all of the devices are subject to -- these Class II devices would be subject to MDR requirements. In other words, there would still be the other requirements in place regarding good manufacturing practices and needing to submit adverse event reporting.

But the question is: do we review the data in the application and review the labeling before it goes to

market?

ACTING CHAIRPERSON McCAULEY: Dr. LoCicero.

DR. LoCICERO: Now, one of the things that we've been hearing all morning is that the FDA has assured us that they would review the information, look at the indications, be sure that the product addresses the specific concerns about health issues related to the indication.

So I think it would be imperative that we make this nonexempt.

ACTING CHAIRPERSON McCAULEY: Any other discussion?

(No response.)

ACTING CHAIRPERSON McCAULEY: Those in favor of making this nonexempt or further devices nonexempt from pre-market notification? Nonexempt.

(Show of hands.)

ACTING CHAIRPERSON McCAULEY: The vote is unanimous for nonexemption.

MR. GATLING: Thank you.

Question 12, existing standards applicable to the device, subassemblies, components or device materials. I don't recall. Were there any referenced in the guidance

document at all?

DR. WITTEN: Yes. There is a biocompatibility standard referenced in the guidance, and you could answer this question just by saying standards referenced in the guidance. That could be your answer to this question.

ACTING CHAIRPERSON McCAULEY: Any objection to the panel for proceeding in that direction of following the special guidance document standards?

Any objections?

(No response.)

ACTING CHAIRPERSON McCAULEY: None.

Does that conclude the supplemental form?

MR. GATLING: Yes. Thank you very much.

ACTING CHAIRPERSON McCAULEY: Okay. Is there a motion to accept the classification work sheet that's filled out with the recommendation of Class II for absorbable hemostatic agents intended as an adjunct to hemostasis when control of bleeding by ligature or conventional procedure is ineffective and impractical?

DR. LANZAFAME: So moved.

DR. LoCICERO: Second.

ACTING CHAIRPERSON McCAULEY: There's a motion

by Dr. Lanzafame and seconded by Dr. LoCicero. Can we have a vote at this time?

All in favor?

(Show of hands.)

ACTING CHAIRPERSON McCAULEY: The vote is unanimous.

The motion of the panel unanimously is that absorbable hemostatic agents intended as an adjunct to hemostasis will control the bleeding by ligature or conventional procedures is ineffective or impractical, to be classified into Class II.

Are there any further discussions?

(No response.)

ACTING CHAIRPERSON McCAULEY: At this point I'd like the panel members to just briefly state why they voted as they did. We'll start with Dr. Lanzafame.

DR. LANZAFAME: I voted in that fashion based on personal experience, the discussion and deliberations today, and also based on the information provided prior to the panel meeting.

ACTING CHAIRPERSON McCAULEY: Dr. Leitch.

DR. LEITCH: I voted this way based on the

review of the information that we were presented, the presentations by the manufacturers, and the long-term use of these agents with good safety and few serious adverse events reported.

DR. CHOTI: I agree. I voted this way based on experience and the information presented.

ACTING CHAIRPERSON McCAULEY: Dr. Blumenstein?

DR. BLUMENSTEIN: I want to note, first of all, this is one of the rare events where the statistician votes with the rest of the panel.

(Laughter.)

DR. BLUMENSTEIN: Second, I voted this way not based on experience because I've never used one of these devices, but I've been assured that the surveillance for future uses and adverse events and so forth is as good as it can be within reason, and I haven't been shown anything that indicates that this shouldn't be reclassified.

ACTING CHAIRPERSON McCAULEY: Dr. Miller?

DR. MILLER: Yes, I voted based also on personal experience and on our discussions today.

ACTING CHAIRPERSON McCAULEY: Dr. LoCicero?

DR. LoCICERO: I voted based on experience, the

information presented today, and a review of the definition of Class III, which these devices no longer meet.

ACTING CHAIRPERSON McCAULEY: That concludes our morning session. We will break and return or reconvene this afternoon at one o'clock.

(Whereupon, at 11:55 a.m., the meeting was recessed for lunch, to reconvene at 1:00 p.m.)

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

(1:08 p.m.)

DR. KRAUSE: Before we get into the official afternoon program, I've asked Dr. Keyvan Farahani of NIH/NCI to come and discuss some new, interesting funding that's available through the Cancer Imaging Program, which may be applicable to some of the devices and some of the research that's going on in the field that's going to be discussed today.

So as soon as they have Dr. Farahani's slides set up, I'm going to ask him to go before we start the official afternoon's session. So just bear with us until we get the computer set up, and then we'll have Dr. Farahani.

(Pause in proceedings.)

DR. FARAHANI: Good afternoon. My name is

Keyvan Farahani. I'm Program Director for Image Guided Diagnosis and Therapy Branch of the Cancer Imaging Program, formerly known as Biomedical Imaging Program of the National Cancer Institute.

I would like to thank Dr. Krause and Schultz for this opportunity to introduce to you an initiative that's going to be announced shortly, in the next few months, that is a program for small business grants for integration and clinical evaluation of technologies for image guided interventions.

I only have a couple of slides that I will go through quickly.

There has been many advances in the last ten years or so in combining imaging with drug or inertial (phonetic) delivery systems that have assimilated the need for development and optimization of these systems for clinical evaluation.

We view image guided interventions as, indeed, separate categories of imagine guided biopsies, image guided surgeries, and image guided therapy.

The majority of research thus far has focused on development of component technologies for various

interventional techniques. So there's a lack of integrated and optimized IgI systems, and that's one of several obstacles in advancement of image guided interventions of cancer.

There's also a realization for complexity of IgI methods that is expected to increase as the new technologies come on line. These technologies include molecular imaging, miniaturized electromechanical systems and robotics.

So we feel that there's a need to extend beyond feasibility trials in some of these techniques.

The purpose of this program announcement is to promote integration of component technologies in image guided interventions and help support their subsequent clinical trials in order to deliver these technologies into the bedside.

So we realize that these tasks of system integration and clinical trials require extended financial support, and this program is designed to do that and meet some of these needs.

The technological scope of this initiative would include integrational, interventional, and monitoring devices onto imaging platforms, such as MRIs, CT, or

ultrasound. The clinical applications would include tumors of solid organs, including brain, lungs, liver, the breast, et cetera.

So with that in mind, I'm here to answer any questions after the program or any time, and there's my contact information. I'll be happy to discuss anything with you.

Thank you.

DR. KRAUSE: Thank you.

ACTING CHAIRPERSON McCAULEY: Good afternoon. I'm Dr. Robert McCauley, and I am Professor of Surgery and Pediatrics at the University of Texas Medical Branch in Galveston and Chief of the Plastic Surgery Services for the Shriners Burns Hospital also in Galveston, Texas.

I'm currently serving as Acting Chairman for this session.

This afternoon the panel will be making recommendations to the Food and Drug Administration regarding clinical concerns involving devices intended to ablate or remove breast tumors.

Since we have new panel members, I'd like to take this time to introduce the panel members who are giving

of their time to help the FDA in these matters and the FDA staff at the table. I'm going to ask each person to introduce him or herself stating his or her specialty, position, institution, and his or her status on the panel as a voting member, industry or consume representative, or deputized voting member.

I would like to start to my right with Dr. LoCicero.

DR. LoCICERO: I'm Jose LoCicero. I am a thoracic surgeon. Currently I am professor and chair of the Department of Surgery at the University of South Alabama, the Director of the Center for Clinical Oncology in the Cancer Research Institute of the University of South Alabama, and I am a deputized voting member.

DR. SOLOMON: I'm Steve Solomon. I'm a radiologist at Johns Hopkins, and I'm a consultant to the panel.

DR. HALBERT: Hi. I'm Francine Halberg. I'm a breast cancer radiation oncologist at the Marin Cancer Institute and clinical associate professor at UCSF, and I'm a consultant to the panel.

DR. KOPANS: I'm Daniel Kopans, Professor of

Radiology at Harvard Medical School and Director of the Breast Imaging Division at the Massachusetts General Hospital, and I'm a consultant to the panel.

DR. BRENNER: Dean Brenner from the University of Michigan, Professor of Internal Medicine and Pharmacology. I'm a medical oncologist and pharmacologist responsible for the Cancer Prevention Program at the University of Michigan Cancer Center.

DR. MILLER: I'm Michael Miller. I'm a Professor of Plastic Surgery at the University of Texas M.D. Anderson Cancer Center, and I'm a member of the panel.

DR. WITTEN: Celia Witten. I'm the Division Director of the Division of General and Restorative and Neurological Devices at the FDA, which is the reviewing division for these products.

MS. BROWN: I'm Debera Brown. I'm the Vice President of Regulatory Affairs for Bronchus Technologies. I'm the industry representative and a non-voting member of the panel.

DR. DOYLE: I'm LeeLee Doyle. I'm the Associate Dean for Continuing Medical Education and Faculty Affairs at the University of Arkansas for Medical Sciences, College of

Medicine. I'm the consumer representative and a non-voting member on the panel.

DR. BLUMENSTEIN: I'm Brent Blumenstein. I'm a biostatistician in private practice. I'm a temporary voting member.

DR. CHOTI: I'm Michael Choti, surgical oncologist at Johns Hopkins Hospital and associate professor of surgery and oncology, and I'm a voting member on the panel.

DR. LEITCH: Marilyn Leitch. I'm a surgical oncologist, Professor of Surgery at UT Southwestern Medical Center in Dallas, the Medical Director for the Center of Breast Care there, and I'm a temporary voting member.

DR. LANZAFAME: Hi. I'm Raymond Lanzafame. I'm a general surgeon. I am the Director of Laser Medicine and Surgery at the Rochester General Hospital in Rochester, New York, and I'm a temporary voting member.

DR. KRAUSE: My name is David Krause, and I'm the Executive Secretary of the panel.

ACTING CHAIRPERSON McCAULEY: We will now proceed with the open public comment session for this afternoon. All persons addressing the panel speak clearly

into the microphone as the transcriptionist is dependent upon this means of providing an accurate record of this meeting.

We are requesting that all persons making statements during the open public hearing session of the meeting disclose whether they have financial interest in any of the medical device companies.

Before making your presentation to the panel, in addition to stating your name and affiliation, please state the nature of your financial interest, if any, and disclose if anyone besides yourself paid for the transportation and accommodations.

We will begin with those individuals who have notified the FDA of their request to present in the open session.

There is none?

DR. WITTEN: No.

ACTING CHAIRPERSON McCAULEY: Okay. Is there anyone else wishing to address the panel at this time?

(No response.)

ACTING CHAIRPERSON McCAULEY: We will now move to the FDA presentation. Dr. Binita Ashar of the FDA is

going to give us a presentation at this time.

Dr. Ashar.

DR. ASHAR: Thank you.

Good afternoon. My name is Binita Ashar, and I'm a general surgeon with FDA's Center for Devices and Radiological Health.

I would like to provide a brief introduction for this afternoon's open session where you will be providing your recommendations regarding clinical trials designed to examine the safety and effectiveness of thermal ablation devices for the local treatment of breast cancer in lieu of local resection.

There are several technologies that have been described in the literature as using a minimally invasive approach to introduce thermal energy into a breast cancer in order to produce irreversible cell damage. These devices include radio frequency ablation, focused microwave, focused ultrasound, interstitial laser photocoagulation, and cryoablation.

Many of these devices have been cleared by the FDA and are marketed for the general indication for soft tissue ablation. For a device to obtain a more specific

indication, however, we expect a clinical study for this new indication demonstrating device safety and effectiveness.

At this time no thermal ablation device has been cleared by the FDA specifically for the treatment of breast cancer. FDA, therefore, is seeking the panel's input regarding clinical studies that may be conducted in order to support such an indication.

We believe that an open forum such as this is the best way to initiate this process, and we wish to thank all of those who are participating in this meeting.

With that, I would like to provide a broad overview of where we have been and possibly where we are going. As you know, in the late 1980s, a number of studies, the largest being the NSABPO6 trial, demonstrated that there was no difference in the disease free and overall survival between patients treated by total mastectomy versus lumpectomy with radiation therapy.

It was these results that began the minimalist era of surgical management of breast cancer in the late 1980s.

In 1996, this panel, the FDA General and Plastic Surgery Devices Panel, convened to discuss the role of

stereotactic breast biopsy devices in the diagnosis of breast cancer.

As an aside to their primary topic, they did briefly touch on some clinical trial issues regarding the use of stereotactic breast biopsy devices for therapeutic breast cancer excision. However, they did not provide a full discussion that can be used to address the issues that we are facing here today.

At that time, the panel felt that patients should not receive therapeutic resection using a stereotactic biopsy device outside of the confines of a controlled clinical trial, and that the ultimate endpoint for such trials would be the local failure in the preserved breast.

The panel discussed the duration of follow-up, and depending on the risk for recurrence, entertained following patients anywhere from two years to 15 years.

The purpose of today's session is threefold. First, we would like the panel to consider the level of evidence that would be required from feasibility studies involving breast cancer thermal ablation followed by open excision before moving to pivotal studies involving breast

cancer thermal ablation without excision and simply following patients for cancer recurrence.

Second, we would like to obtain the panel's recommendations regarding the framework for pivotal studies examining the safety and effectiveness of thermal ablation devices for ablating breast cancer in lieu of local resection.

Finally, as treatment of patients with breast cancer today involves a multi-disciplinary approach, we would like the panel to comment on the effects of thermal ablation when combined with radiation therapy, chemotherapy, and radiographic evaluations.

Oftentimes when a device is demonstrated as safe and effective in one population, efforts are made to expand the use of the technology to a broader population of patients. For example, in your discussion today, you could focus on cancers less than two centimeters having a low risk for recurrence.

However, how would your recommendations change if the tumor, for example, was larger than two centimeters with a more aggressive histology?

Therefore, for each of the following questions

please remember to make recommendations specifying the appropriate patient population and discuss under which circumstances repeat initial feasibility studies of ablation followed by open resection should again be undertaken prior to extrapolating the results to a broader patient group.

You have all been given the questions that FDA has requested that you address during this discussion, and these questions are provided on the subsequent slides. I will run through them briefly here, and then Dr. McCauley can take over the presentation.

This first question deals with the level of evidence that would be required in moving from a feasibility study that treats the breast cancer by ablation followed by resection to a pivotal trial that treats the breast cancer by ablation in lieu of resection.

The second question addresses the pivotal trial framework for studies aimed to demonstrate thermal ablation device efficacy in providing local breast cancer treatment in lieu of lumpectomy.

The third question deals with the effect of thermal ablation on the surrounding tissue affecting the chemo and radiosensitivity of the surrounding tissue.

And the final question deals with the ability to radiographically follow the tumor during the time of treatment and subsequently after receiving a thermal ablation.

Thank you very much for you attention, and I will turn the discussion over to Dr. McCauley.

ACTING CHAIRPERSON McCAULEY: Thank you, Dr. Ashar.

Are there any questions for Dr. Ashar? Yes.

DR. KOPANS: Just on your last point, it shouldn't just be to radiographically follow, but to follow by imaging because ultrasound is effective, MRI is effective as well.

DR. ASHAR: Excuse me. Yes, it would be including all radiographic modalities.

ACTING CHAIRPERSON McCAULEY: Any further questions?

(No response.)

ACTING CHAIRPERSON McCAULEY: We will hear from some members of industry with regards to this topic. Will the representative, Mr. George Burditt, from Kelsey, Incorporated please begin your presentation?

MR. BURDITT: Dr. McCauley, Dr. Witten, Dr. Krause, and members of this very distinguished panel, my name is George Burditt, and I've been asked to be the spokesman for a group of experts representing Kelsey, and for the record, of course, we're all being paid by Kelsey. I'm not sure a lawyer needs to tell you he's being paid, but I must admit I'm being paid for this presentation.

The other members of this panel of experts that I've had the pleasure of working with are Dr. Kambiz Dowlatshahi, M.D., F.A.C.S, professor at Rush Presbyterian Medical School. He introduced stereotactic core needle biopsy to the United States. He has pioneered interstitial laser therapy for breast cancer treatment and is a leader in this field.

Phil Lavin is a biostatistician, an eminent biostatistician particularly in the field of the subject we're talking about today, clinical studies for devices.

Chris Brauer, former of the Office of Device Evaluation, is also an expert in this field, particularly concentrating in women's health issues, which are, of course, so important in the subject that you all are considering today.

Dave West, who is with ODE for many years, as I'm sure you know, and his associate Chris Sloan, who is with us here today or consulting with us, they are both now with Quintiles.

And we also are pleased to have Linda Jewel of Siemens here with whom we're working closely and Tyco has been working with us.

And I must saw as a lawyer who has been practicing food and drug law for 50 years, I'm particularly pleased to have such an outstanding group of experts supporting me in this whole project.

As I poignantly know from personal experience, the most dreadful sentence a woman can hear is, "You have breast cancer." My wife heard that sentence when she was 39 years old, and in those days she had the state-of-the-art treatment, which is mastectomy with excision of the axillary nodes, and that was accepted as the method of treatment.

Since that time detection methods have increased substantially. As the Society for Women's Health Research said, as you can see in this slide, breast cancer really gives women a double dose of fear, of course fear of dying, but then equally important, the fear of disfigurement from

treatment.

This slide shows the incidence of detection of small breast cancers. The only application of ILT is for breast cancers of 1.5 centimeters or less. So we're talking about small cancers here.

This slide, which is from a 1990 study, shows that in 1990, 25 percent of the tumors detected in women's breasts were one centimeter or less, and Dr. Dowlatshahi thinks that now that figure 13 years later is probably nearer 50 percent.

The developments in detection of breast cancer, all of the things that have just been mentioned, the ultrasound, color Doppler ultrasound, developments in mammography, all of these other diagnostic and detection procedures have been developed enormously over the last few years as you all are well aware.

But the treatment of breast cancer has not followed suit. It simply has lagged behind, and as the National Cancer Policy Board said, serious problems exist with the quality of cancer care provided to women with breast cancer in the United States.

There was a Time magazine article that expressed

this same dichotomy between the development of breast diagnosis and treatment of breast cancer, and Dr. Gralow from Hutchinson said, "We may be far over treating our patients," and that's particularly true because of the increase in the percentage of the small tumors.

Let me turn now to this ILT treatment specifically. It's a new treatment option. It is clearly not a universal replacement for lumpectomy. Lumpectomy does have defects, as you are well aware. There are risks with it.

I saw one study that over a period of 20 years lumpectomy with radiation and with chemo had a 20 percent failure rate after 20 years, and without any supplementary treatment it had a failure rate of 40 percent.

Women in the United States deserve an alternative to a procedure that has a failure rate as high as that.

Here's a diagram of the device, and Dr. Dowlatshahi, who is an expert with lasers, is going to focus the laser on that slide so that you can see specifically the things I'm talking about.

Using stereotactic imaging, the location of the

tumor is precisely determined. That's the blue in the center.

Small metal markers are inserted in the periphery of the tumor for accurate visualization and follow-up. Those are those five little black points that you can see.

Two needles are inserted into the breast, one bearing the laser probe -- that's the one on the left -- together with fluid infusion at the tip to keep it cool, not over 100 degrees Centigrade, and the other bearing the temperature monitoring probe. That's the one that has the five dots on it.

Stereotactic imaging confirms the proper placement of the needles. The doctor is watching the whole placement of the needle on his screen.

Power supplied to maintain the central temperature of 80 degrees to 100 degrees Centigrade during treatment.

Well, I pushed something here, and I haven't the slightest idea what I pushed. Help.

Dr. Lavin is not only an expert in biostatistics, but he's also an expert in -- thank you, Tim.

Thank you, Phil. Sorry. Beg your pardon.

But power is applied to maintain the central temperature in the core at between 80 and 100 degrees Centigrade, never over 100, and the saline solution I mentioned is on the tip to make sure it doesn't go over 100, and the surgeon has real time monitoring through five sensors, with the five sensors that you can see throughout the 2.5 centimeter sphere.

The procedure is automated. It has continuous control through the procedure. The surgeon is in complete control of it. You end up with a transcript of the treatment and a patient record.

The great advantage of this is that it's replicable, evaluable, and controllable. It's a standardized procedure.

After the procedure axillary node biopsy is performed, and radiation and chemotherapy is administered as needed, just as it is now.

This is a chart that shows one of the things that the surgeon is looking at during the procedure. This is a display. The left column, the tall one with the red at the top of it, is the temperature inside in the center of

the tumor.

The five bars are the temperatures recorded by each of those five sensing points on the needle, which you saw in the diagram. This is an example of the control the surgeon has when he's administering this procedure.

These are mammographic images, pre-ILT on the left, post ILT on the right.

This is a color Doppler ultrasound, which to me was very impressive. On the left it shows the blood vessel feeding the tumor right in the center. The white is the blood vessel. On the right the blood vessel is gone. This is post treatment, right after treatment. There's no delay in this. It is after treatment. As you can see, the blood vessel has been totally ablated.

Let me switch now to patient selection for the study. This is a list of at least some of the criteria that we would propose that you consider in your recommendations and which we would like to propose to the agency.

The lesion, as I said before, must be not greater than 1.5 centimeters.

In situ or invasive cancer must be established by core needle biopsy.

The lesion has to be well defined and clearly visualized so that you will have that .5 centimeter zone around the tumor.

There's no radiotherapy or chemo applied before because that would throw it off.

And the baseline diagnostic mammograms, ultrasound, color Doppler ultrasound would be taken prior to treatment.

How do you know if that damned spot is out, as Shakespeare might have said with this process? One month following the treatment, the patient is examined thoroughly, mammogram, ultrasound, color Doppler ultrasound, core needle biopsies of the treated tumor at the center and at three, six, nine and 12 o'clock positions, and pathological examination of the tissues taken from the core needle biopsies.

As far as follow-up and monitoring is concerned, we would propose three, six, nine, and 12 months follow-up for everybody in the study with a mammogram, ultrasound, and if there's any area suspicious anywhere in the tumor, additional core needle biopsies would be performed, and of course, everyone would go through annual

screening mammography thereafter.

As far as investigators, and this is also very important because it may be unique for this particular kind of a study, experience breast specialists only would be enrolled as the investigators. They must be experts at image guided core needle biopsy.

Dr. Dowlatshahi will personally train every one of them, detailed training in the operation of the device and procedure, and the initial procedures by the investigators would be supervised. Dr. Dowlatshahi is going to actually go to the center where every one of these investigators is performing his work and at least the first, and maybe more than one, but at least the first one, Dr. Dowlatshahi will personally participate in the therapy, and hopefully that will show that there will undoubtedly be at the beginning a resection of at least the first one.

And incidentally, I should thank Dr. Ashar for her beautiful presentation to you all. That was most helpful and certainly spells out the issues that you will be facing.

We would hope that you would not require because of the circumstances of this whole situation a separate

feasibility study followed by a separate pivotal study. We would propose that you run in the feasibility study into the pivotal study bey requiring, as we propose to do, that the first patient, at least the first and maybe more than one, not only have the ILT, but also have a lumpectomy, and that will help establish the efficacy. It will help establish the training has been successful. It will give everybody the comfort factor that you would normally get with a feasibility study.

But this laser is not a new event. As you're well aware, lasers are used in all parts of the body now, and this is the first time it has been proposed for use in treating breast cancer, but it's not like it's bringing something off the moon all of a sudden to use a procedure that's never been used before. It's a well established procedure, and the laser that's being used is a well established laser. Hopefully it will show the ablation of the tumor and the half a centimeter margin rounded.

For clinical trials we would propose a multi-center study obviously to test for effectiveness, and in this particular circumstance, patient satisfaction and cosmesis, which are really far more important in a study

like this and for this kind of a device than for most surgical devices. The clinical trials would collect safety data on every facet of safety that's known to mankind, adverse events, failures, local recurrence, everything that would normally be done, and it's very important not only to Kelsey, but to everyone in the United States that we have a total safety report.

Hopefully this would demonstrate that the tumor has been ablated and that the patient satisfaction is guaranteed with the procedure and with breast appearance, and again, because of this unique procedure, because of the quality of life.

We propose that you consider that we have a one-year study one year after the last patient is enrolled so that every patient in the study would have at least one year of treatment. As a matter of fact, everybody would have more than one year except for the last patient enrolled. So while it's one year, it's one year only starting with -- the year doesn't start until the last patient is enrolled.

My own personal feeling, this is probably the most important slide of all. We propose a long-term post market follow-up of all treated patients for 20 years. That

is, in a sense because we're asking for the one year period for the pivotal study, but we want to make sure that 20 years later this process is successful.

Incidentally, 20 years is also what's the number in 20-year studies on lumpectomy. So it would give us something to compare.

The long-term follow-up would include a registry of all treated patients, keeping track of everybody. I'm in a registry like that for another medical device. So I know it works. There are registries like this. It's not a new concept, but it would be applied to this specific device.

And the registry and the follow-up would include new patients admitted to the study post clearance. It would not stop just with those enrolled in the first year.

Ladies and gentlemen, thank you very much. ILT is a major step in the treatment of breast cancer. It will help close the gap between the huge advances in detection and the relative inaction in the field of treatment of breast cancer.

It has been a great pleasure for me to see these experts and to listen to them and hear them explaining all of the benefits of this to women throughout the United

States, and we urge you to consider these very carefully. We know you will. We appreciate very much the action of the FDA in picking such an outstanding panel to hear us.

We'll be here all afternoon if you have any questions of any of we. We'd be delighted to try to answer.

Thank you very much.

ACTING CHAIRPERSON McCAULEY: Thank you, Mr. Burditt.

Do we have any questions from the panel regarding this presentation.

DR. KOPANS: More of a comment. I'm not sure there's actually an answer. I think it's important to realize that stereotactic guidance, the actual anterior and posterior margins of the lesion are not determinable using stereotaxis. So I assume that the technology is being used with the thought that there will be a spherical volume of ablation, and you're assuming that the anterior and posterior margins are going to be within that sphere.

I think there's a little bit of question whether that's going to be true or not.

MR. BURDITT: A very good question. We've tried to address it in a couple of ways. One is it will only be a

defined tumor. If it's one of these tumors that's kind of splattered around, not eligible for the study; won't be included.

Second, because of the follow-up and because of these enormously improved detection methods, if anything is missed, there's always the possibility of going back in and doing a lumpectomy or any other procedure that's necessary.

Furthermore, it's anticipated that there will be radiation and chemo as there is with lumpectomies. We're not trying to avoid that. Those will still be in there. So that's certainly something that Dr. Dowlatshahi is very well aware of. That's why he's proposing half a centimeter margin beyond what you can see as the end of the tumor.

But you're right. Tumors are irregular in shape, and therefore, we're trying to reach that question by focusing specifically on these smaller tumors that are well defined.

Thank you, sir.

ACTING CHAIRPERSON McCAULEY: Dr. Lanzafame.

DR. LANZAFAME: Yes. Can you provide some further detail on the spacing between the thermal probe and the laser probe?

And secondarily, I'm assuming that the process is a photothermal process and is also related to the wavelength. Given that fact, do you have any specific information on the scattering characteristics of the metallic clips and the thermal probe?

MR. BURDITT: On the first question, the needles are parallel, as you can see in the diagram. They will be a millimeter or a millimeter and a half apart, but parallel. As a matter of fact, Dr. Dowlatshahi did one just the other day under his IRB approval, and the first time the second needle didn't go in right, and they had to modify the second needle.

Incidentally, the lady was totally satisfied.

DR. LANZAFAME: So in other words, the thermocouple is one millimeter away from the laser source and not at the edge of the sphere as it's shown in the diagram? Am I understanding that correctly?

MR. BURDITT: Kambiz.

DR. DOWLATSHAHI: George, I think I'd better step in.

MR. BURDITT: I appreciate.

DR. DOWLATSHAHI: Thank you for your great

presentation.

Regarding the distance between the two needles, currently we're using one centimeter in order to give that zone of ablation. The eventual size of the zone of ablation is about two and a half centimeters in diameter, between two and a half to three centimeters, which will encompass the 1.5 centimeters.

Going back to your question regarding the effect of the laser beam on the metal markers, these are steel markers which are used for carotid inclusion. I don't think it is going to affect the reflection. Is that what you were saying?

DR. LANZAFAME: Actually it's the other way around. Is there a scattering or interference?

In other words, one issue would be black body absorption, which is what I think you're addressing. The other would be scattering or shadowing at the opposite end relative to your source, whether it's spherical or cylindrical.

DR. DOWLATSHAHI: In terms of you mean affecting the coagulation of the tissue?

DR. LANZAFAME: Right.

DR. DOWLATSHAHI: I have not seen that happen. In practice, the only 54 patients that I treated and removed serial resection by a pathologist did not show any escape or failure of the malignant cells around the markers.

I think Dr. Kopans has one question.

ACTING CHAIRPERSON McCAULEY: Dr. Blumenstein.

DR. BLUMENSTEIN: So there's a point here where you use the term "post marketing." So I assume that this is your registration trail that you've described here.

DR. DOWLATSHAHI: Yes.

DR. BLUMENSTEIN: So I failed to identify the primary endpoint. I didn't see anything about a sample size, and I gather this is not a randomized study. So what is your reference data? What is your criterion for success?

MR. BURDITT: It is not a randomized study. We're proposing a single arm study. I like to think in my terms that you don't really need a control group. How would you get a control group? You can't have a group of people who aren't going to be treated. That would obviously be unethical.

To have a group of people on a particular treatment that's in existence doesn't really serve much

purpose. The test is: is it successful? And we're proposing a Bayesian type study that would focus on this group only.

We have not talked about numbers. The reason we haven't is that we want to discuss this matter very carefully with FDA. Of course, we have numbers in mind. They're a little confidential, for one thing, but we also want to discuss with FDA what FDA thinks is a reasonable number to have in the study.

We want to discuss the number centers, the number at each center. This equipment is quite expensive, and we can't have 50 centers. In the first place, Dr. Dowlatshahi is going to train everybody at every center, and it's not feasible to have that many.

It will be a few centers carefully selected with experienced physicians, and the number at each center we'll work out with FDA in our proposal.

ACTING CHAIRPERSON McCAULEY: Dr. Brenner.

DR. BRENNER: So in your design, if I've got it right, you're going to do re-needle biopsies, but you're not going to resect because I presume you've already published that. Is that what you're suggesting?

And if so, if that's true, if I got you right, then how do you know that you actually ablated beyond a centimeter or half centimeter margin that you're claiming to ablate for a regulatory endpoint?

I'm confused.

MR. BURDITT: Well, the answer lies in all of these enormously improved diagnostic detection techniques. The physician is going to be looking at this regularly, one month with a careful follow-up with all of the diagnostic tools that we know about, and regularly throughout the year so that we can answer these questions.

We don't believe there will be any splatter or anything caused by the five markers. We don't believe that anything is going to happen. Dr. Dowlatshahi has not seen them in the 54 patients he has done, and what we plan to do is watch carefully for those things.

That's an excellent question. That's obviously the kind of thing we have to watch about.

DR. BRENNER: So your argument is that the imaging is sufficient to rule out any kind of cells that are viable; that the imaging will pick all of that up. Is that your argument?

MR. BURDITT: Yes, sir.

DR. BRENNER: Thank you.

MR. BURDITT: And it will be continually improving. Even that advanced procedure isn't stopping.

Yes, sir.

DR. KOPANS: Well, just as an imager, that doesn't work. There's no imaging test that really can accurately tell you. Certainly microscopic disease and even fairly gross disease may be viable, and there's no imaging test that can tell you its viability or nonviability.

I do have a question. You're saying that you're going to have a thermal injury of three centimeters, two and a half to three centimeters in diameter. Breasts in compression in stereotactic devices, I haven't looked at the numbers, but they're down around four centimeters that allow biopsy.

What kind of distance do you need for the lesion to be from the skin surfaces so that you don't affect the skin surfaces?

DR. DOWLATSHAHI: One centimeter.

DR. KOPANS: One centimeter at both ends? Because that's kind of triple the number of individuals you

can treat.

DR. DOWLATSHAHI: I realize that, but I think if the lesion is close to the skin, it's possible to cool the skin by ice or by spray, and that's, in fact, what I have done in the past. In the far posterior part of the lesion close to the chest wall, that, again, has not been any problem, but I think the point that you're raising is correct. The small breasted women who in compressed form will have the thickness between the skin, the front and the back reduced significantly may not be suitable for this, but in practice we have not had any burns on either side.

DR. KOPANS: The other point, again, for the panel is that when you're doing a stereotactic positioning of anything, the lesion doesn't always fit in the center of the compressed volume. So you may have a four centimeter thick breast, but the lesion could be a half a centimeter from the anterior-posterior skin.

So just another issue that you're going to have to deal with.

DR. DOWLATSHAHI: But my response to that was that that may well be true. I agree with you, but there has not been any scalding of the skin apart from the very early

days when the fluid dripped back onto the skin.

Now we're quite aware of that, and we take care of it by cooling the skin. In fact, there's going to be a thermal sensor on the skin.

DR. KOPANS: Just one more follow-on. Sorry.

And that is that one of the things I haven't seen in the reports on the various ablation technologies is really evidence that cosmesis is preserved. I mean, I take your word for it. I just wonder though if this amount of heating even just under the skin, if the skin is preserved, do you end up with puckering and so on?

I would suggest that there be some way that you monitor the cosmetic results in any of the tests that are done.

DR. DOWLATSHAHI: The patients will be photographs before and after. The break has not occurred, except in one case in my experience, and this is, of course, the patient who has had treatment and been followed up. Those early 54 cases, they all underwent lumpectomy or mastectomy.

ACTING CHAIRPERSON McCAULEY: Dr. Brenner.

DR. BRENNER: Well, pursuing the cosmesis

endpoint since that seems to be a major theme in all of these presentations and documents, I'd like the speakers if they could to address the question of whether or not there's a validated, reproducible method of measuring cosmesis for the breast as an outcome because that seemed to be problematic, at least to me.

DR. DOWLATSHAHI: I think that that is correct. As I said, the photographic or the taking pictures from the breast before and after surgery or after treatment is one way. I think there are some other methods of developing the patient's satisfaction is probably going to be also an issue here, which is something to be considering.

I don't have a definite answer for you right now.

DR. BRENNER: I think the radiation oncologists and perhaps the plastic surgeons might have -- I know there are scales that have been used. I don't know the validation for those, but it might be something to discuss with those folks.

DR. HALBERG: Sir Dr. Harris Tarvard (phonetic) has written extensively on assessing cosmesis after radiation therapy, and I'm sure those same scales could be

used in your work.

Since I have the microphone, could I ask a question at this point?

ACTING CHAIRPERSON McCAULEY: Sure.

DR. HALBERG: I was wondering if you have information from the color Doppler ultrasound about the blood flow in the tissue immediately adjacent to the ablated zone.

DR. DOWLATSHAHI: Immediately afterwards there is increased flow to the vessels surrounding the ablated area. There is hyperemic, as you expect, intense hyperemia which is shown by color Doppler. We usually wait for a few days for that reaction to subside before evaluating the tumor.

So what I can tell you for sure is that the vascularity of the tumor is abolished totally. Sometimes the tumor does not have much vascularity, and we enhance that by giving an enhancing agent, such as --

DR. HALBERG: I was actually more interested in maybe a month out after the initial hyperemic and increased blood flow changes, if there's a zone of decreased blood flow that you're left with. I don't know if you've done

those color Dopplers prior to lumpectomy and how long you've waited, you know, what your longest interval has been from the doing the laser treatment to the lumpectomy.

But I'd be interested in the longer term blood flow in that region.

DR. DOWLATSHAHI: The longer term, if we look at these two or four weeks or even six weeks, it diminishes. The flow, the amount of flow in the vessels diminishes, but undoubtedly there is a cut point between the vessels in the normal unablated tissue and the ablated tissue.

DR. HALBERG: So the transition zone with decreased blood flow then adjacent to the area of necrosis long term?

DR. DOWLATSHAHI: Long term there is definitely a decrease.

DR. HALBERG: Thank you.

ACTING CHAIRPERSON McCAULEY: Dr. Solomon.

DR. SOLOMON: In your lumpectomy specimens, what has been the consistency and size of the ablated zone? Has it been something that's reproducible given the power setting that you're using?

DR. DOWLATSHAHI: The series that we removed

dated the interval between the treatment and the removal was between three to four days all the way up to eight weeks, and you do see the changes in terms of the acute necrosis. The pathology is a little bit more detailed. If you wish I can give you the several zones.

Very close to the laser you get what you call a wind effect. Further away from the laser there is an area what we call pseudo necrosis. With HME you don't get any -- it looks as though it's non-treated. Further away, one millimeter away or three millimeter away, you get total necrosis. Further away you get hyperemia with fat necrosis. So you have concentric circles of about two to three millimeters from the center, which is the laser point.

DR. SOLOMON: But do you ever get smaller ones in the sense that, you know, if you do a particular patient can you count on it always being two centimeters in diameter or is it possible that some patient it's only one centimeter? Because that's going to be crucial for doing an image guided procedure.

DR. DOWLATSHAHI: Quite right. It depends on the amount of laser energy you give. In other words, if you give about 3,000 joules, you may get up to about one and a

half or two. If you give eight or 9,000 joules of energy, you may get about 3,000. I'm sorry. Three centimeters.

Therefore, there is a titration between the amount of energy and the size of coagulation.

DR. SOLOMON: And when you've looked at these patients on a separate topic of cosmesis after ablation, is there a hard nodule or something that they can feel after the procedure in terms of scar?

DR. DOWLATSHAHI: Immediately after the procedure there is a swelling. If the tumor was nonpalpable, the patient feels a swelling or fullness rather in the area. We give them ice packs for the next six to 12 hours, and the patient feels the fullness which may become even a lump over the next six to 12 weeks, and then subsequently this will decrease and disappear, and that mass is actually the changes you see on the mammography.

ACTING CHAIRPERSON McCAULEY: Dr. Kopans?

DR. KOPANS: Just a follow-up on the issue that Dr. Halberg brought up, and that is that if, in fact, the blood supply to the tissue surrounding the ablated tumor is compromised, that could conceivably influence the effect of radiation to any residual tumor nest that may still be

viable in the area.

So, you know, killing the blood supply is a good thing if you get all of the tumor. It may not be a good thing if it's compromised at the time of radiation therapy.

DR. DOWLATSHAHI: I think that that has a valid theoretical point. In the cases that have been treated in this way and not removed, I have one patient who has now gone for three and a half years. The tumor, which was eight millimeters, was totally ablated, and she developed a small oil (phonetic) cyst at one year, which I aspirated without any necrotic tissue in it. In fact, I have three patients like that. The tumors are ranging from seven millimeters to 14 millimeters, and at one year at the cyst which was the residual evidence of cancer there was about one, one and a half centimeters, which was evacuated subcutaneously.

DR. KOPANS: If I could just make a follow-on point to what Dr. Solomon was, I think, getting at, and that is that the recurrence rates that we're seeing now following lumpectomy surgical excision with negative margins and radiation, our recurrence rates are down around two percent at about eight to ten years, much lower than what was reported in BO6, for example.

So modern surgery, modern radiation has really reduced the recurrence rates even lower than what's in the literature, and I would urge FDA to perhaps look at more modern series as a reference point.

And I think the improvement is due to the fact that we really are looking for negative margins, and the concern that I think some of us have on the panel is if you're not removing the tumor, you don't know that you've got negative margins, and so you have to have an ablation technique that somehow as close as you can will assure that you've gotten all of the macroscopic margins.

Of course, the reason for radiation is that you can never be sure that you get all of the tumor even with surgery, but I'd had to go backwards where we're seeing a marked decrease, a decrease in mortality from breast cancer due to imaging early detection and I think better therapeutic techniques, and I think we just need to be careful not to lose some of the ground that we've gained.

DR. DOWLATSHAHI: I think the question of margin has been extensively evaluated recently. There was a very good review by the N.D. Anderson group. The difference in the recurrence between eight millimeters and five

millimeters and three millimeters and one millimeters did not seem to be significant.

If you have cancer right at the point of resection that seems to be true. That seems to be important.

If I address the question of the markings intraoperatively as a surgeon myself, as well as others who are in the field, we always depend on the tactile sense to achieve about at least four or five millimeters of normal tissues surrounding what we regard to be a cancer.

I think by imaging it is possible to evaluate that much, much better. I think there is a fairly good correlation between the tumor size by imaging, ultrasound or mammography, versus pathology. I think it's close to 80 percent judging by the papers that I have read and judging by my own experience.

So I think the imaging by mammography and ultrasound will give you a good idea of the extensions of the tumor. Remember that we are going to be very selective in the inclusion of the cases for this study, especially when we can see the tumor as a clear moon in the sky. Those are the ones that we're going to choose initially for this

treatment, and to exclude those with the extensive intraductile carcinoma, as represented by micro calcifications for even necessary by MRI.

DR. KOPANS: But we can't lose sight of the fact that modern therapy has been, I think, more successful because it's predicated on negative pathological margins. We can't feel the margins of a tumor, certainly the microscopic margins even at surgery, and the issue of extensive intraductile cancer is also a problem because not all intraductile cancer calcifies, and so you can have extensive DCIS at the periphery of a tumor that's not evident by imaging, not evident even at the time of surgery, but the pathologist says that the margin is grossly involved.

Those lesions you won't know about until they recur.

DR. DOWLATSHAHI: But I would like to challenge you, Dr. Kopans, with regard to the pathology being gold standard. I don't think that is 100 percent true because it depends on the pain of the knife of the resident who usually bisects these tumors and reports that the largest diameter or the margin was clear or not clear, may not be in that

knife.

In other words, the knife might have gone this and the other side of that positive margin.

ACTING CHAIRPERSON McCAULEY: Do we have any other industry representatives that wish to address the panel at this time?

(No response.)

ACTING CHAIRPERSON McCAULEY: I would like the panel to keep in mind that we're talking more specifically about general clinical issues regarding nonsurgical ablation of breast tumors. We do have some questions that we'll have to answer that were presented to us by Dr. Ashar, but we'll take a 15 minutes break and we'll come back and address those questions.

(Whereupon, the foregoing matter went off the record at 2:08 p.m. and went back on the record at 2:25 p.m.)

DR. KRAUSE: Neil, could you put up the first question, please?

ACTING CHAIRPERSON McCAULEY: This is the first question which the panel is asked to address for the FDA. That question states: please characterize the appropriate

level of evidence or confidence level that will be required to move from a feasibility study that treats breast cancer by ablation followed by resection to a pivotal trial that treats the breast cancer by ablation in lieu of resection. Include in your discussion the following issues: accuracy of the device to target the specific lesion, completeness of ablation, reproducibility of different investigators, and reproducibility amongst different centers.

We'll start with -- is there a lead reviewer for this question?

DR. ASHAR: I believe Dr. Leitch was going to be starting with us.

ACTING CHAIRPERSON McCAULEY: Dr. Leitch.

DR. LEITCH: Well, with respect to this question, I think the confidence level we want, first of all, is that we can document that there is successful ablation of all viable tumor, and I think patients would like 100 percent confidence level, and that may not be technically feasible to get, but I would say somewhere 95 percent to 100 percent evidence of complete ablation in a feasibility study.

And one of the studies we have for review by ISO

describes a 96 percent total ablation rate in that series. That series is small, 26 patients, I believe; microwave; 80 percent response rate, but measured in sort of different ways, not necessarily a pathologic complete ablation.

Dr. Dowlatshahi's studies, you know, originally 70 percent complete ablation, and then ultimately in later cases higher rates of complete ablation, but of course, that represents an experience over time and working out the bugs of a procedure.

So within that, you want to have confidence that the tumor, in fact, is ablated by whatever method of ablation is chosen, and the targeting techniques, I think we have a lot of evidence from the biopsy literature about successive targeting with respect to stereotactic radiographic imaging, as well as ultrasound.

I think a more difficult technology for trying to target the lesion would be that of MRI. While it's good to define a lesion, there are still some issues on how to target with that device.

So I think, one, you've got to figure out what technology in a given investigator's hands works the best in terms of achieving ablation, and you know, we have a number

of types to review, and so that would be one thing I think the FDA would want to address.

In terms of margins, if the lesion is not removed, you're not going to have any sense of what the margin is other than what you estimate it by some imaging technique with respect to the changes that occur in the environment of the tumor. That's the only way you're going to be able to evaluate a margin.

And it sounds like the investigators have looked at trying to ablate anywhere from five to ten millimeters beyond the visible lesion. You know, in surgery we had that pathologic evaluation of what the margin is, the exact width, but again, to be fair to the ablationist, the margins have been debated in the surgical literature as well, being quite narrow in an NSABP trial with not cut across tumor cells versus the Milan trial with quadrantectomy type wide resection.

So while we can't make such a big thing exactly about the width of margins, you're asking different questions about margins in the ablation without resection versus a surgical specimen which is removed and has a measurement of the tumor from the edge.

So I think what one would have to get is from the resected data of ablation, what does it appear to be the width beyond the evidence tumor on imaging that you have to have your technique impact in order to end up with ablation of the entire lesion.

Then with respect to reproducibility, again, having the technology that a lot of people are able to do because breast cancer is frequent. These small tumors are very frequent, and you can't have it be the case that only five centers in the U.S. know how to do this if you're going to have it be implemented as an important technique in breast cancer care.

So the technology would have to be evolved in a way that it could be broadly applicable. I think from a surgical perspective, ultrasound imaging approaches would be more broadly applicable in the surgical community than MRI certainly, and there are certainly issues in MRI imaging and the significance of findings that are debated just in looking at MRI for our current methods of treatment of breast cancer.

So that has a way to go, although it may turn out to be one of the more accurate technologies.

So those would be my comments to kind of get things started.

DR. WITTEN: Before you go around -- I'm sorry. Are you going to ask everyone else to add?

ACTING CHAIRPERSON McCAULEY: Yes.

DR. WITTEN: Can I just clarify part of what that question means? Is that okay?

ACTING CHAIRPERSON McCAULEY: Yes.

DR. LEITCH: That would be good.

DR. WITTEN: Okay. Yes. Just in case it's not entirely clear, what our current thinking has been is that we want to make sure the sponsor, before we approve a large scale pivotal trial, our current thinking is that the sponsor would need to show that they can ablate the cancer or the tumor predictably according to a certain predictability by performing an ablation and then followed by a resection.

And so that leaves us with a dilemma of, you know, say we wanted that as a feasibility study; then our dilemma is what degree of success for a feasibility study would leave us happy to approve a pivotal study, given a high rate of success as was pointed out of, you know,

treatment of breast cancer with conventional methods.

So, I mean, we've heard from one sponsor their suggestion that a feasibility study is not necessary, and of course, you might agree with that point of view and you could comment on that also, but in terms of our thinking, we'd want a feasibility study where a sponsor performs an ablation and then resects the lesion to look at how well they did in their ablation. How would we characterize success of that feasibility study or what would we want to look for?

And I think you've, in part, answered that, Dr. Leitch, by suggesting, you know, 96 percent, but I just want to make sure that everyone understands that that is part of our question. It's about our lack of comfort about knowing when it would be okay to move from one stage of product development to the next stage.

ACTING CHAIRPERSON McCAULEY: I have one question for you, Dr. Leitch, and that question actually is addressed to the tumor size that you think would be applicable to this type of therapy.

DR. LEITCH: Well, I think what, you know, the investigators have shown us is that their level of

confidence -- and this is true in some of the other types as well -- is probably under two centimeters, and they're probably picked this 1.5 centimeter to be sure you're not, you know, 2.1 or, you know, that you're really sort of, you know, well within that T1 tumor size.

And then the limitations which have been pointed out with respect to the zone of whatever ablative technique, for example, in a stereotactic device where the breast is compressed front to back, this width is going to be limited by that way the breast is fixed.

So, you know, again, if you've got a big tumor that is, you know, essentially filling the compression device, you can't apply these heat related technologies because you don't have the margin width front and back.

So having a small tumor in a large breast, you know, lets you do some of the planning, the treatment planning that would get you the dimensions on all sides, not just four sides, but also anterior and posterior, you know, having six dimensions covered by the ablative field, but not have a complication related to that because you don't really have that width.

So they're suggesting smaller tumors. Now, that

makes it less valuable, in my opinion, because a 1.5 centimeter tumor surgically resected from the breast and the breast looks pretty good when you get finished, and so, you know, the advantage to the patient of this technology for that size tumor I think is going to be relatively low.

Where we need more help actually is on the people who are more difficult to achieve breast preservation, who, you know, we think they have a small tumor; we resect them; their margins are positive, what we were talking about with the DCIS at the margin. Where the patient really desires breast preservation, some of these techniques might be used to, quote, clean up the margins and help with this periphery of tumor.

But applying it in the very small tumors, the benefits for endpoints, if we want to look at, of, say, cosmesis, local recurrence which is going to be low in the standard therapy in that group of patients and the cosmesis which is very high in those patients, you know, to demonstrate a significant difference in those is going to be very low.

So while those small tumors may work best for the achievement of ablation, which I think is true, and it

would be safest, the question is: well, what benefit do you get out of having done it on a smaller tumor size?

ACTING CHAIRPERSON McCAULEY: Dr. Choti.

DR. CHOTI: I think that a feasibility study, an ablate and resect feasibility study, well designed is going to be important information before moving forward to a pivotal trial, and how that feasibility study is done is going to be important.

One issue, and probably a small tumor ablate and resect is the way to go; one issue that will come up in the feasibility study is the ethical aspect of the lumpectomy because it may be that the lumpectomy will actually need to be or will end up being larger in that woman on that feasibility study than the lumpectomy she may have gotten if she wasn't in the trial. So that's something that the sponsors will need to address.

Alternatively, it could be an ablate and resect in the mastectomy situation, which would be a clean study, but there's a select number of patients in whom she may have a small tumor and yet require a mastectomy.

But that perhaps is one way a feasibility study could be designed.

As far as the endpoints for the feasibility study, difficult. If it's designed where the resection is done immediately after the ablation, then the -- well, if the resection is done several days later or a week after an ablation, then the number you end up with 96 percent necrosis may be more accurate than in an ablate and resect in which the resection is done immediately after the ablation, particularly in cryotherapy and others when you don't see immediate histologic destruction of the cells.

And so certainly after cryoablation, the tumor looks totally viable. So it's difficult to access completeness in some therapies.

In heat thermal ablation it's easier immediately, but even then NADA staining and some other parameters may need to be done to assess percent necrosis.

The advantage though of an immediate ablate and resect feasibility study is that this question of the margins perhaps could be more easily assessed because you often, I think, in breast as in other soft tissue, you may still be able to see the tumor or histologically tell the tumor versus normal breast. So you may be able to more clearly assess the true margin and the ability of targeting.

How accurate the center of the ablation zone is relative to the center of the tumor will give you some feasibility information about the accuracy of targeting.

ACTING CHAIRPERSON McCAULEY: Dr. Blumenstein.

DR. BLUMENSTEIN: I take this question to mean that you really want a number, and one number was suggested. I think you said 95 percent, did you say?

DR. LEITCH: For ablation, tumor ablation.

DR. BLUMENSTEIN: For ablation. Well, it seems like we have to start with what is the definition of ablation, and that has to be completely standardized across all possible studies of this type, and I'm not sure how to do that. I'm just a statistician, but you know, in other words, I assume you're talking about a resection with some kind of inspection of the margins, the surgical margins, and the definition of what represents success versus failure.

And that's going to be difficult, but it seems to me on the other side of that, once you have that definition it isn't a matter of how much success you have but what constitutes failure, and I think you said 95 percent success. That's just something you threw out.

I play this game all the time when I try to work

on trial sizes and so forth, but what the other half of that is what constitutes failure. Is it 80 percent, 85 percent or 90 percent?

And that has a lot to do with how large of a study one is going to have to do. If it's 90 percent failure, 95 percent success and you're setting up a trial to distinguish between those two hypotheses, it's going to be a pretty large trial.

And so I think that, you know, we need to worry about what constitutes failure and what constitutes success, not just what constitutes success.

I can also read this question in a very general way, and I might as well get this off my chest. It says here, "Was appropriate level of evidence to move on to a pivotal trial," and one of the things I'm worried about when I look at these methodologies is all of the new things that are going on with respect to using the tumor and characteristics of the tumor with respect to various assays, microarray analyses and so on like that.

What are we doing in this case because we're not getting the tumor? What are we missing? And what are we missing because we're not doing ancillary lymph node

dissection and other things like that?

I don't know these things. I'm asking more as rhetorical questions because I hang around breast cancer enough to know that a lot of people think these things are important.

And then there's one more question I have, and that is what about autologous tumor vaccines, which seems to be an up and coming idea. And so feasibility to move on would also seem to me to be what is it that you're precluding by using this kind of a therapy as opposed to one that actually harvests the tumor or harvests the tumor plus nodes or whatever other things are there.

ACTING CHAIRPERSON McCAULEY: Dr. Doyle.

DR. LEITCH: Did you have a comment? Go ahead.

DR. DOYLE: As neither an expert in oncology nor sort of a Dick and Jane on statistics compared to my companion on the right, one thing that strikes me is that if this is something to replace the lumpectomy, then the completeness of ablation, it would seem to me, should be the same as the completeness of ablation in lumpectomy. So whatever is acceptable for lumpectomy would seem to me to be the minimal confidence interval we would accept for the

completeness of ablation by any other technique.

ACTING CHAIRPERSON McCAULEY: Ms. Brown, any comments?

MS. BROWN: Coming back to Dr. Blumenstein's comment about the confidence interval for a feasibility study, a 95 percent confidence level would imply a pretty large group. So my experience is feasibility studies tend to be smaller studies, but they lead to a pivotal study.

So I was curious what we have in mind in terms of some numbers of patients in the feasibility study leading on to a pivotal trial.

DR. LEITCH: Well, I think for, you know, a single institution, you know, you might be able to do something in sort of the 50 to 100, but you also have to kind of look at the capability to do this broadly, and so I think what some of the people that are looking at this are trying to do are to get, you know, at least more than one institution participating at the same time to demonstrate that you can do this.

And so one theory would be if you had a center that maybe had done 50 cases, where they had resected and they wanted to do this broader trial, that the other

institutions under their tutelage would need to demonstrate, and my thought would be somewhere in the range of ten to 20 cases where they had ablation rates of 100 percent.

I don't think one case is sufficient to say, "Well, you know, we did one case and that was 100 percent ablated." I think you would need to demonstrate with some number, and Brent can maybe give us a better idea about what that would be, but, you know, for that part I don't think it has to be hundreds.

Obviously when you get to comparing it, you know, without resection, then you're talking that you've got to have very large numbers of patients.

DR. BLUMENSTEIN: Yeah, I mean, I'll just throw out some numbers, and I think Robert made a very good point here about the idea that if you are doing this kind of study it's really multiple institutions. So when we're doing a very small study across multiple institutions, it doesn't really fly very well.

But if your definition of success was 95 percent and your definition of what constituted failure is 80 percent, then you would require about 40 patients or so. But if you fail to find success, then really what you're

saying is that there's no evidence that it's 80 percent or more.

Is that success? And so the question is that you really have to talk about that spread, the difference between what constitutes success and what's your evidence of non-success.

ACTING CHAIRPERSON McCAULEY: Dr. Miller.

DR. MILLER: I think the task of the surgeon is to ablate the tumor, and if these technologies ablate the tumor, then they can compete with an open resection, but they have to 100 percent, I think, ablative. I think anything less than that they lose, and so I think that the feasibility needs to compare this as an ablative procedure and with an immediate resection afterwards, with a 100 percent tumor ablation with the alternative procedure.

And if an investigator proves he can do that, then I don't see why that particular investigator is to be held back from doing a pivotal study because now the whole question shifts from are you ablating the tumor properly to what is the biological course of the disease if you ablate the tumor in this way.

And so continuing to do feasibility studies for

somebody who proves they can ablate the tumor completely with this technology, that is not productive unless you just move right on, and this will get to what happens to the disease if you use this approach.

So I think I could envision a study where, you know, you had everybody go through a period of time where they prove they can completely resect the tumor with whatever technology we're talking about here, in which they do that for a requisite number of patients.

Then you go right into the next phase with a pivotal study, and you just sort of conduct the whole thing at the same time. I could see something designed like that, and it would address all of these questions.

And I don't know what number to pick, but I know that for sentinel lymph node mapping the magic number is 20. If a surgeon wants to start doing sentinel lymph node mapping, if he does 20 successful mappings and lymph node dissections, then he start doing mapping. So perhaps something analogous to that got this.

DR. HALBERG: Can I ask a question?

How important do you think it would be for the surgeon or the investigator performing the thermal ablation

to do the lumpectomy immediately following the ablative procedure? I mean if they did it within a week or a couple of weeks would that make a difference to you?

DR. MILLER: I don' know. I think either immediately -- I guess I don't know what happens to those tissues once you ablate them like this. I think the quicker the feedback the better.

If the tissue changes so that you can't tell where you did your procedure, that would be a problem, I guess, but either immediately or if it's reasonable to wait, then maybe a few days, but I think promptly to do a resection procedure after you try this approach to confirm that you are getting a 100 percent ablation with your technique.

DR. SOLOMON: Pathologically it can be difficult to assess ablation immediately after the ablation. So it may take 48 hours or longer until you can actually see histologically the changes.

DR. MILLER: Okay. So I don't know if that's important then to wait the right amount of time to be sure that you check it properly, but the other thing about this that I'm aware of is that the biggest problem with it is

localizing the tumor, and the misfires -- at least I know in the radio frequency studies, there was 100 percent tumor ablation if the tumor was where you ablated. If you didn't ablate where the tumor was, then the tumor survived.

So the problem wasn't getting an ablation where you put the device, but it was properly locating the device. And so I think, you know, if the study is designed so that the imaging method is as accurate as possible, then that will be an important part, too.

ACTING CHAIRPERSON McCAULEY: I think that the comment I have here is that even with the imaging devices that we currently have, there are still going to be times when you're not going to be in the tumor. so you still have to count that as a failure.

DR. MILLER: No question about. I think it becomes a question of patient selection.

ACTING CHAIRPERSON McCAULEY: Dr. Dowlatshahi has told us that just recently he had a problem with a case. So he's very experienced.

DR. MILLER: Yeah, I think that becomes a question of selection. I mean, if you cannot identify on your imaging a discrete tumor, if you do a core biopsy and

cannot confirm that that tumor is a type which tends to stay discrete and doesn't tend to be multi-focal or have diffuse spread, like not lobular carcinoma, not VCIS, all of these things, but you can confirm it's a discrete tumor; you can identify it with confidence on your imaging; then that patient is a candidate.

If they fail any of those criteria, then they're not a candidate. So I think just careful selection and then complete ablation with the alternative, that makes sense to me.

ACTING CHAIRPERSON McCAULEY: Dr. Brenner.

DR. BRENNER: Trying to advise the agency on this issue, you know, we're talking about T1 tumors here really. They're small. It's conceivable that most of this disease is a systemic control problem, not a local control problem. Certainly at this size I think it's important to recognize that.

So this question is real important because it really is a core issue in terms of local control.

So the way I would advise the agency in terms of dealing with the design of Question No. 1 is the point out a number of variables I think you need to look after.

One that has not been mentioned here is a pathology protocol. In other words, everybody is talking about complete ablation, but how do you define that pathologically? And I think there has to be a standardized pathology protocol that is doable and validated across institutions and documented concordance amongst pathologists so that when somebody says, "It's ablated. It's ablated," and that there's not that variation -- for example, if you take out a two centimeter lesion, depending on the sectioning, you might miss islands of tumor, and I think that's one advice I have for the agency to be concerned.

The second advice I have is, as has already been pointed out, this has to be multi-institutional and has to deal with cross-culture. In other words, different places do things differently. That has to be in some way dealt with and standardized, and I recommend that the agency recommend that.

The third issue is cohorts and the type of cohorts, and the question that arises in my mind is the T2 lesion and whether or not that should be inclusive in such a design. I would probably set some cutoff that the technology allows, and T2, I think, includes up to five

centimeters. That might be too big.

So I think you need to be careful about the size of the lesion that's being ablated, and that needs to be standardized.

And then I think that in terms of endpoints, definition, what endpoints are we talking about? As I thought about it, there would be a pathologic endpoint. In other words, complete pathologic ablation, and then there would be a pathologic partial ablation endpoint, and the way one might have to look at that might be a surface area indication and one would want to utilize perhaps a volumetric surface area indication, and that would be used as a quantitative endpoint in order to then deal with the questions, particularly the two latter questions, the reproducibility amongst different investigators and reproducibility among different centers.

You've got to standardize the pathology. You've got to standardize your surface area in terms of the amount that's being ablated, and then you can do the reproducibility work and get a quantitative endpoint that Brent can then work with. Because I think that's the kind of information you need in order to say, "Well, we're 85

percent successful," or, "we're 96 percent," 95 percent. You need that kind of data.

So basically we're looking at pathology bins, but I also think you need imaging bins. In other words, is there also an image outcome? Would there be an image pathologic outcome and also an imaging partial outcome?

And I'm wondering. A partial response outcome and an imaging might actually be fibrosis and not tumor, and so that's some information that I think would need to be dealt with, but those are the variables that I think the agency needs to look at in the design of a preliminary trial that I've not seen in the literature to date that I would want to look for before I approve a pivotal trial.

Then in terms of endpoints, in terms of ablation, I think my surgical colleagues are much better qualified to comment than I am on this. However, I think that in terms of concordance data I'd like to see a concordance of about 90 percent at least for both imaging, as well as pathologic outcomes to insure that we know what we're doing going into a pivotal trial amongst different institutions.

And I'd like to see a coefficient variation of

around ten percent. Why ten percent? Well, that's what we use in analytics when we want to validate an analytical procedure.

And here I think the coefficient variations are much larger, and one could take issue with me on that, and I'd like Brent's comments on whether that's a reasonable coefficient variation in terms of outcomes.

So those are the solid, perhaps regulatory kinds of points that I tried to make in terms of responding to the agency's question.

ACTING CHAIRPERSON McCAULEY: Dr. Kopans.

DR. KOPANS: Yeah, a lot of the points that I wanted to make have already been said, but let me just reinforce a couple of them.

First of all, I think it would be very important to talk in detail to medical oncologists and radiation oncologists. The point that was brought up, how much information do they need to provide modern care as we're now talking about tailoring everyone's tumor therapy to their particular tumor. We're not removing the tumor. The point that was made earlier, we may be losing that information.

I think it's important for people who don't do

core biopsies or needle biopsies to realize that there's a very big sampling error with needle biopsies, and what is the definition that you're going to accept of adequate core biopsy? Is it spring loaded devices? Is it vacuum assisted devices? Is it en bloc resections, whatever?

That really I haven't seen any real definition or standardization of what is a sufficient biopsy and how much information is either being lost or is sufficient, I guess, to adequately treat the tumor.

I think, again, margins have been emphasized over and over again. I just want people to have a realistic understanding that imaging does a very good job in defining tumors, but it does not define microscopic margins, and ductile carcinoma in situ is variably imaged even with magnetic resonance, which is probably the most sensitive certainly to invasive cancers. At least 50 percent of DCIS doesn't show up on MRI.

And for those of you who haven't been around as long as some of us have been, we thought that extensive intraductile cancer was a major risk for recurrence based on the Joint Center experience a number of years ago, and then it was realized that there was residual tumor. The margins

were not clear, and it wasn't so much just that there was extensive DCIS in the tumor.

You need to be sure that you've got the vast amount of tumor out before radiation therapy can be adequate. So, again, margins is a real tough nut to crack. I would be of the school that if you're going to replace an excisional biopsy with in vivo ablation, that you need pretty close to 100 percent certainty that you're ablating what the surgeon would have taken out.

And that's going to be a little tricky because there's really no standardization of what the surgeon takes out and what is a negative margin. The NSABP, you know, says if there wasn't a cell touching the margin, that's a negative margin. Mel Silverstein would say a one centimeter margin is probably what is required. So that's going to take some definition.

Also, some things to keep in mind. In modern therapy, my understanding is that recurrences in conservatively treated patients don't really start showing up until about two years. So that to have just a two-year follow up to me is insufficient to know what your recurrence rates are going to be.

I would say a minimum of five years. You could argue even longer periods. I kind of like the idea of a long-term registry that was mentioned earlier. That becomes logistically extremely difficult, I would imagine, but you need to follow these patients up for the long term.

And then, again, to come back, you have to have 100 percent clear margins. How many cases that takes, I guess it's an infinite number if you want 100 percent. So I'll defer to the statistician to determine the exact number.

And then finally, a point that was brought up that I think needs to just be kept in the back of our minds, and that is, you know, the reason our recurrence rates are so low in conservatively treated breasts are because (a) good surgical technique and (b) good radiation therapy.

And is tissue damage to the residual breast where there may be nests of cancer cells that escape the ablative technique, are those cells because of hypoxia in that tissue going to be more resistant to radiation and are we, therefore, going to see more recurrences maybe further down the line?

So, again, a whole bunch of issues I don't have

the answers for at this time.

ACTING CHAIRPERSON McCAULEY: Dr. Halberg.

DR. HALBERG: There are four things I want to expand a little bit on. The first would be that when one does the study we're going to assess margins, if you will, not just by imaging, but by core biopsies. All of the information we're going to get on the tumors is going to be from core biopsies, and at least one of the RF papers discussed getting a series of core biopsies all around the edge of the tumor.

I think in the initial feasibility study it would be important to specify how one wanted to obtain core biopsies and standardize that as well. (a) You'll obtain more tissue. (b) You'll get some margin status information that you could then use to help guide the subsequent pivotal studies.

I would encourage the protocol for the biopsies prior, in the first study as well, so that you can understand what you're doing with respect to imaging and lumpectomy.

The second point that I wanted to make is that, of course, the group that one envisions the thermal ablation

devices working best for are the T1 tumors, but I would encourage us to try and look at the largest and ugliest tumors that one can still ablate.

In other words, where it's pretty well documented that the recurrence rates at ten years with standard lumpectomy, negative margins, radiation therapy are at most five or six percent and at experienced breast centers probably closer to two to four percent. So those are very, very low recurrence rates, and those recurrences are usually not seen until five years.

Having 1,000 patients with very small tumors, following them for five years and seeing no recurrences doesn't mean that you're successful. It just means that you haven't followed enough patients out long enough.

So I would encourage us to look at the larger end of the spectrum in terms of patients both in the initial study and I don't know. You know, we'll have to look at what the limits of these technologies are, but certainly try and push things towards the larger end so that if we see recurrences, we'll tend to see more of them and see them earlier.

The third point that I wanted to make, and this

gets into Dr. Kopans brought up hypoxia, and we'll discuss that much more extensively under Question 4, but I think we have to address this hypoxia in the initial study as well.

Very briefly, any time you perturb the microenvironment in tissue, you perturb the blood supply and create hypoxia, and indeed, the ultrasound data that was presented with laser suggests that you do create hypoxia.

So the short version is that hypoxia is well documented to induce radiation resistance. Radiation doesn't work as well on tissue that's hypoxic, period.

There are a series of elegant studies done many years ago by a gentleman named Roland Holland, who looked at lumpectomy followed by -- lumpectomy negative margins in patients who then went on and had an immediate mastectomy. And what he did is he cut in every last breast cell and microtomed, and found that even with lumpectomy negative margins where you think you've, quote, gotten it all, there are a substantial number of patients that have occult satellite little residual microscopic foci of breast cancer left behind, and the vast majority of that residual disease is within two centimeters of the lumpectomy cavity.

And if that is, indeed, hypoxism that you're

creating, you worry that the excellent results that we're seeing with lumpectomy followed by radiation therapy may be compromised by some of these thermal ablation devices.

So I think one of the endpoints, even the initial study has to be not just local recurrence, but I'd like to see us look at survival and distant disease free survival as well. The question raised there is does local recurrence impact distant metastatic disease, and that's controversial with breast conserving therapy.

What is also of concern, however, is that there's an increasing body of data suggesting that hypoxia changes the phenotype of cancer in general; that if you render cancer cells hypoxic, you increase their genetic instability. You increase their metastatic potential. You increase the aggressiveness of cancer.

And so what you'd want to do, even in the initial study, is track these patients to see if there is a higher distant disease recurrence. I would encourage that to be one of the endpoints, as well.

And those are basically the points I wanted to add.

ACTING CHAIRPERSON McCAULEY: Dr. Solomon.

DR. SOLOMON: I agree with what the panel has been suggesting, that we're talking about a 95 percent or higher success rate, but there are three other points that I'd like to just emphasize that are a little bit different than other people have been talking about.

The first is to recognize, again, the limitations of imaging. Recent studies have shown that even if you biopsy and actually remove all of the ultrasound visible tumor so that you can't see anything left, there's residual tumor.

So that stresses the importance of margins and that you have an acceptable wide margin of ablation beyond just seeing the lesion that you're looking at.

The second point is that the placement of the needle is critical, and there are a lot of very operator dependent issues in this particular procedure, and, therefore, again, you would want something that would be multi-operator, a multi-center trial to emphasize the reproducibility in more than one person, in more than several people's hands.

And the third point that I want to emphasize is that when you do an ablation, except for, let's say, MR

thermometry in that unique case of focused ultrasound in the MR scanner, you really can't tell what the kill zone is. You can't see on ultrasound exactly where you -- you can't define exactly where the kill zone is.

And, therefore, I think in the lumpectomy study, it will be important to look at the size of the ablation zone, the necrosis zone and link that to a particular amount of power or settings on the machine so that you can have a reproducible -- because you can't tell when to stop.

The biggest problem is when do I stop ablating. So it's important that you know that, okay, I'm looking at a one centimeter tumor. The needle is placed in the right spot. I know if I do 50 watts for X amount of time the ablation zone is going to be two centimeters or whatever, and that's going to give me a wide enough margin of error, and that's why the pathology on this lumpectomy study and the size of the lesion and the reproducibility of the lesion is going to be important.

DR. HALBERG: I apologize. There was one other point I wanted to make on the initial study, and that is that if one is doing a lumpectomy several days or longer after the initial ablative procedure there are ways to

assess the hypoxic zone, and it may be important to document that.

There is a commercially available kit called a hypoxia probe. Basically what they do is they give small doses of a nitroimidazole compound 24 hours prior to the lumpectomy, and then you can use antibodies to stain the lumpectomy specimen to see the zone of hypoxia that has been created, and at least on a limited basis that might be an interesting sort of surrogate marker for the hypoxic problems you might see down the line.

ACTING CHAIRPERSON McCAULEY: Dr. LoCicero.

DR. LoCICERO: A lot of points have already been covered. Concerning immediate lumpectomy, we know that from other ablative studies that there can be trapped viable tumor cells within an ablated specimen, and so we main need to have more time to know what cells have died and what cells may survive.

Another potential is over time with ablative therapies you can see the line of demarcation very well around four to six weeks after ablative therapy, and that might be an easy marker for the pathologist. In fact, it may be good to have a pathologist experienced in examination

of ablative tumors provide some information to the FDA.

Concerning reproducibility of the investigators and the site, I think we already have several guidelines for that. Some years ago the Lung Cancer Study Group set out guidelines for lung cancer resection and lymphadenectomy.

More recently, we have the NCCTG, the North Central Cancer Treatment Group, certifying surgeons to perform laproscopic assisted colectomies. We have the information from individuals performing sentinel node biopsies, and the American College of Surgeons' Oncology Group certification of surgeons performing thoracoscopy.

So any of those could be used as models to develop guidelines for certifying surgeons and sites to be entered into a study like this.

You're definitely going to need to have a very dedicated monitor for any study like this.

ACTING CHAIRPERSON McCAULEY: Dr. Lanzafame.

DR. LANZAFAME: A number of points have been made already, but if I can be a little bit of a purist, I have a problem with the word "ablation." Ablation to me means gone immediately, removal of a volume of tissue.

We're not doing that. We're causing coagulative

thermal necrosis be it by light energy, by radio frequency, ultrasound, by some methodology, and we're leaving that in situ in a living organism.

Bearing that in mind, there's a long history of experimental studies, some of which our own, some of which a lot brighter minds have done, talking about what that might do to the host in terms of sensitizing the host, improving some parameters, making other parameters worse, rendering tissue hypoxic.

But having said that, I think we have to keep in mind that we're not physically removing tumor at least with these modalities unless we specify on the part of FDA that that's going to be done as part of the trial.

And in terms of things such as reproducibility, we have to understand that breast tissue is certainly not homogeneous in nature, nor are the tumors homogeneous in nature. Presumably we would want to stipulate that we had solid tumors. We've alluded to some of that, but I think that would be very important.

We also have to understand that age, composition of breast varies, and we would at least want to be looking at data as to whether or not we're stratifying patient

populations along those sorts of endpoints.

That becomes particularly important with our thermal source, light, energy absorbed in tissue. The tissue will change as it's undergoing its thermal denaturation. Presumably that's also occurring with the other energy sources.

And so I think we have to be very circumspect in terms of how we do that.

We've talked about imaging methods and reproducibility thereof. To the best of my understanding, any of the things that we're considering or are about to consider are actually using standard available technologies to do the imaging for us.

Having said that, I think we would want to stipulate very narrow boundaries in terms of what type of device, manufacture of device, particularly if we're talking about a technology that's going to be applied to a stereotactic stage on someone's machinery.

We probably would want to be doing some site testing in phantoms and otherwise to be certain that we're actually getting what we think we're getting with the device.

And if we're talking about things like fibers and other sources, particularly if there are things that are being used for different purposes, we may actually want to track that particular delivery device to be certain that its configuration is actually producing the dosimetry that we think it is.

Indeed, there's been a lot of discussion about pathologic margins. As somebody who's done that sort of stuff on whole organisms and human populations, the ability to guarantee 100 percent resectability or to verify that by the pathologist will probably take a century. We are looking at a sample of something that we assume is a 360 degree sphere. So folks have looked at a certain number of sections.

I think it would be naive of us to hold this group of technologies any differently than we do surgical technologies in that respect. I think one of the reasons that we got into the issue of looking at margins is that those of us that put our fingers in there and manipulate things are spreading cells around and doing other things. So I think there's a crude surrogate for our inability to guarantee by some other means that we're outside of that.

We're looking at the width of a margin or a pseudo margin of a deformable specimen.

One of the issues in terms of looking at our endpoints may actually be along the lines as Dr. Halberg alluded to, and that would be, for example, to do periodic sampling of that site if that site is left in situ in the patient, i.e., periodic stereotactic biopsies at prespecified locations and in prespecified numbers.

ACTING CHAIRPERSON McCAULEY: Thank you.

DR. KOPANS: Can I make a quick comment on the margin issue and pathology?

I think the point is well taken that our gold standard -- and I think it was brought up by the company as well -- of pathologic analysis of margins is far from perfect. If it were perfect, we wouldn't need to do radiation. So I think or I hope that's understood.

The pathologic analysis that should be required of these technologies should be some kind of standard pathologic analysis. Now, that said, I'm not sure there is a standard pathologic analysis, but the FDA maybe needs to define what is the pathologic analysis that should be the standard for surgical specimens and the ablative, or

whatever we're going to call it, technologies should have to live up to that standard.

ACTING CHAIRPERSON McCAULEY: Dr. Witten, we've had an extensive of this first question with numerous views. It would be impossible for me to summarize them all at this time.

However, I think that if you feel we have provided you with enough information to proceed to the next question, I propose that we do that.

DR. WITTEN: Yes. Thank you.

ACTING CHAIRPERSON McCAULEY: Could we have the second question, please?

The second question states: please provide a pivotal trial framework for studies aiming to demonstrate thermal ablation device efficacy in providing local breast cancer treatment in lieu of lumpectomy. Please address the appropriate patient population with respect to primary tumor size, nodal status, histology, mammographic findings, ultrasound findings, biological markers, age, et cetera.

Some of these issues have already been addressed, but we'll briefly go through them again.

Number two, control group. Again, this was also

partially addressed in Question 1. Assessment in terms of radiographic modalities, biopsies, et cetera, and the frequency of such assessments.

Duration of follow-up to demonstrate efficacy of treatment in lieu of lumpectomy.

The lead discussion panel member, again, for this question, is Dr. Leitch.

DR. LEITCH: Well, you know, I think ultimately to demonstrate the benefit of this that would need to be a randomized trial comparing it to the standard treatment.

However, I think before that is done there does need to be a trial that would simply be a single arm trial taking patients with ablation, not resected, and looking at a number of issues in those patients before taking it to the randomized trial environment.

And, again, we've talked about the tumor size issue, which from a safety perspective would be more in the T1 tumor size, but it's also a size where we're less likely to demonstrate, you know, a significant advantage, but you know, it would be a safer group of patients; that the tumors are well demarcated by the imaging technology that's selected for targeting, whether that be mammography or

ultrasound; that there are not extensive associated calcifications with the lesion.

With respect to age, I think you want the patient at least to have a life expectancy of five years so that one could have the opportunity to monitor outcomes. I personally would not particularly put any restrictions on the tumor profile, but would emphasize that, of course, all of those parameters must be obtained before the tumor is ablated in order to guide other therapies.

The other issue which we really haven't talked about is the failure to accurately stage the patient because you do not have pathologic staging of the tumor size, which when you get into these small size tumors the recommendations regarding adjuvant therapy begin to spin on the precise sizing and, you know, maybe the medical oncologists can speak to that as well.

And the control group for this type of trial, I think, would need to be some of the more modern studies, but even then SABP and their more recent trials indicate about a six percent local recurrence rate at ten years, and you could use those types of study as your historical control to look at these issues.

Radiographic assessments. In my opinion, at a minimum, again, this would be kind of whatever you select, but I'd probably be inclined to select both mammography and ultrasound as sort of the standard things that would be done in all patients, and doing that at six months intervals, and I probably would pick a five-year period of duration.

MRI would probably be done as sort of a pilot type of study within some of that population to look at issues of can you measure things like hypoxia and get sort of a dynamic picture of the breast after these types of therapies and maybe answer some of these questions about the zone of hypoxia. So MRI not probably for everybody, but for some subset of that patient population to look at that technology in the long-term follow-up.

Because, again, I think you have got to say how are we going to be able to apply this forever, and hopefully we would be able to do the follow-up by more standard imaging, which would be mammography.

And in my view the follow-up should be at least five years for this type of a study.

ACTING CHAIRPERSON McCAULEY: Thank you, Dr. Leitch.

Dr. Lanzafame.

DR. LANZAFAME: I have nothing to add.

DR. WITTEN: Can I ask a question of Dr. Leitch?

DR. LEITCH: Yes.

DR. WITTEN: Before you go on?

I'm just wondering. You said that you thought there should be another study before the pivotal study, and so I'm just wondering what we would learn from what stage.

DR. LEITCH: Well, the question is what you're going to call a pivotal study.. You know, if you're going to say, well, we're going to take it from we did the ablation and we verified the ablation, you know, and now we're going to take it to where we don't do anything further. We just do the ablation and then we compare it against standard therapy.

To me that's sort of the bigger jump. You could do that. You could do that, but essentially we have no follow-up of any of these people with ablation only to know what the outcomes of those patients are. To then apply it in what I would think would be a very large trial, would it not, for numbers?

So that's the down side of not doing, you know,

a smaller study that looks at some of these issues where you might make a decision, you know, it's not worthwhile to go forward with that.

ACTING CHAIRPERSON McCAULEY: I assume what you're saying then is that the actual framework for a pivotal study really is based on standardization of the feasibility study and the results of that study as we define as being successful, which includes not only a recurrence rate, but also detection and standardization of determining what is true ablation.

DR. LEITCH: I mean, the other things which we haven't really brought up yet, I thought a radiation oncologist might, but you know, there's other things that are coming down the pike in terms of radiation treatment for breast cancer which is, you know, partial breast radiation techniques which may rely very heavily on these issues about hypoxia and that sort of thing, and so that's kind of coming down the pike at the same time this is, and how do you integrate those two technologies?

And the other technology which is an advance in our breast cancer care is sentinel node biopsy technologies, which as I was understanding from the presentation here,

that technique is done after the ablative procedure, and I'm wondering how the ablative procedure might alter lymphatic drainage from the primary tumor so that you're mapping might be interfered with.

And we certainly don't want to jeopardize that technology which we think is a real advance for breast cancer care. So that's another thing you have to take into account because, again, in these very small tumors, all of that data, you know, that sentinel node data becomes very important. You know, the tumor size issues are very -- you know, the exact tumor size issues are very important.

So those things have to be considered in this, which I suppose all of those things could be fleshed out in a randomized trial, but the question is really whether you want to make that kind of commitment and maybe Brent can tell us what kind of commitment that would be in terms of patient numbers, you know, if you went on to the randomized trial.

ACTING CHAIRPERSON McCAULEY: Dr. Blumenstein.

DR. BLUMENSTEIN: Yeah, I mean, first of all, this would have to be a non-inferiority trial. You're not trying to prove that this new ablation method is superior to

standard therapy, but you're trying to show that it's not inferior.

And as a result of that, it's going to be a little bit larger than a trial that's perceived to be a superiority trial. I would say that we would be talking about at least 2,000 patients or more for a trial like this.

I was curious about the control arm and, in fact, the experimental arm in this case. Would there be radiation therapy in both arms or one of the arms?

DR. LEITCH: Well, I think as it has been proposed by the current investigators, it is that they would apply radiation therapy after the ablation. Of course, that may be a more interesting question of could you ablate only and not radiate the patient.

But you know, again, you've got to kind of do the first thing before you could take that out. So you would be, in my thought, you would be doing ablation plus radiation, surgery plus radiation.

DR. BLUMENSTEIN: Yeah, but I mean, what has been said here by your proposal of doing an intermediate trial between the trial addressed in Question 1 and this trial, a single arm efficacy trial which is more like a

Phase 2 drug trial where your primary endpoint is some preliminary evidence of efficacy to justify going to a pivotal trial.

There's also all of these other issues about whether you're using it in combination with radiation therapy or not, and so forth. So all of these things are extremely important at this design phase.

ACTING CHAIRPERSON McCAULEY: Dr. Witten, do you have any further comments?

DR. WITTEN: I don't. I stopped you before you went around the room though. So other people might.

ACTING CHAIRPERSON McCAULEY: Dr. LoCicero?

DR. LoCICERO: No additional comments.

ACTING CHAIRPERSON McCAULEY: Dr. Solomon?

DR. SOLOMON: I agree with what was already said, but the only other twist perhaps for people to think about would be what if this technology were addressed to a positive node group. So these are people who we know that the margins are -- it has already spread to the nodes and the margin positivity may not be as -- we're not as sensitive to that as a safety issue. So that may be something for people to discuss as well.

DR. LEITCH: Yeah, it's sort of the opposite theory that you, you know, pick people that have sort of less to lose than a person who has a high probability of being cured by standard therapy. You know, you pick somebody who has less likelihood so they don't lose as much as the person who is highly curable by current techniques.

ACTING CHAIRPERSON McCAULEY: Dr. Halberg.

DR. HALBERG: In thinking about this question, I realize that a great deal of thought has gone into a very similar trial. The NSAP is in the final stages of a review of a trial that is going to compare lumpectomy with negative margins, and then patients will be randomized to whole breast radiation therapy or partial breast radiation therapy, with the outcome being local recurrence.

And that's really not so dissimilar to a study that would look at thermal ablation alone versus lumpectomy with negative margins to be followed by radiation therapy.

I would encourage the use of radiation therapy in any of these trials because there are a number of prospective randomized trials, at least seven well conducted trials, that show a distinct superiority to the addition of radiation therapy even after wide lumpectomy.

And so I think that that would confuse the issue greatly and increase the risk of recurrence in women if you considered the thermal ablation alone. I don't believe that's being proposed.

So I think we can go back to the NSABP trial. There the proponents of partial breast radiation therapy wanted to look at favorable T1 tumors, women that were generally a little bit older, estrogen receptor positive, no DCIS, well circumscribed tumors, less than two centimeters tumors. They wanted to pick a very favorable group of women and to look at radiating less than the entire breast and to see if that was comparable to whole breast radiation therapy.

So they looked at what it would take to do that. They used a six percent. They basically felt that the recurrence risk for patients with T1 tumors at ten years was six percent based on the NSABP data that we've heard.

And then you have to ask yourself. You know, breast cancer affects hundreds of thousands of American women a year. What kind of increased recurrence risk are we willing to accept in an equivalency trial?

And they thought that a doubling of a recurrence

risk, 100 percent increase, was too much. So they thought a 50 percent increase might be reasonable. In a T1 tumor, that would increase your risk at ten years from six percent to nine percent.

To conduct that study a prospective randomized trial would have to have 6,300 patients followed for ten years because you hardly start to see recurrences in these patients until five years. So length of follow-up is very important in these studies, and it has to be a long length of follow-up.

It is considered too expensive and unrealistic to have a 6,300 woman study, and so, therefore, although it wasn't the first choice of the NSABP investigators, and this isn't finalized either yet, but what will probably come out is a study that includes node positive women, three centimeters and less and including virtually any tumor type so that the recurrence rate of ten years is at least ten percent, and there wouldn't be more than a 15 percent recurrence risk in these women.

And I think that that's quite a parallel situation to the situation that we have here. However, I think that there is actually the potential to do much

greater harm in the women we study here. Again, we have a technology or breast cancer treatment which works very, lumpectomy with negative margins followed by radiation therapy, and we know that the outcomes are excellent in terms of local control.

We are now looking at technology which is going to create an area, a zone of hypoxia in the area that's most likely to harbor residual occult breast cancer cells. We are likely to make those cells radioresistant, and we have the potential at least theoretically to increase the metastatic potential.

So I think it's very important that we conduct an excellent, large study with long-term follow-up on these patients.

ACTING CHAIRPERSON McCAULEY: Dr. Kopans.

DR. KOPANS: Yeah, I really have nothing to add. I think all of the comments have been very good.

Just one point. I'm not sure I made to clear before. Radiographic, just in terms of semantics, means X-ray imaging. So if you're going to talk about imaging modalities, get rid of the radiographic part and put in "imaging" in whatever you write.

ACTING CHAIRPERSON McCAULEY: Dr. Brenner.

DR. BRENNER: I wrestled with exactly the same problems that Dr. Halberg wrestled with: size of the trial, the fact that it would have to be an equivalency trial, and what the endpoints would be of an equivalency trial, and the fact that really if your endpoint is local recurrence, that in fact you have to do at least ten-year follow-up.

And that seemed to me to be something that was really not feasible. So then the question was what would be feasible. My concern with the node positive study's ten-year follow-up endpoint depends, of course, how many nodes because you would expect with node positive patients that a substantial number of them were going to recur and might not have ten-year follow-ups. Whereas in the node negatives you would have more likely that ten-year follow-up.

So I came down on the side of node negatives rather than the node positives, and the reason is that this is about local control, and really local control is different from systemic control, and coming at a medical oncologist, I'm not entirely convinced that there's a huge relationship between local and systemic control in this disease.

And, therefore, one might be able to design a trial, and this would really be up more on Brent's alley than mine, where even at a five-year point one might be able to demonstrate sufficient difference between the arm one could identify some type of confidence interval that would be defined as worse and, therefore, cut the trial, equivalency trial, that might allow you to shorten the trial and, therefore, make it feasible.

So that's where I came down. I came down on a 20 percent change and the 95 percent confidence level towards the worst as the endpoint, the hypothesis you want to test, and didn't calculate the numbers because I figured Brent would and agreed with Dr. Halberg that you couldn't ignore the radiation even though I would prefer to.

I mean, without radiation you're just going to have more events, and the data suggests that that doesn't impact on survival too much or at all, and so, therefore, you might be able to get away with it, but I suspect that you probably couldn't.

I mean, it probably wasn't a doable study because IRBs would probably balk at the idea because standard of care in the community remains, I believe,

radiation, and patients would probably not be willing to enter the study. So you'd have trouble with recruitment.

So I think that that design fails from just a practical point of view. So I come down on the node negative rather than the node positive, but otherwise mainly the same concerns Dr. Halberg has.

Now, people have been mentioning that the medical oncologists should talk about some of the things you need in tissue. It's I guess on the medical oncologist. I think out of a needle biopsy, for the most part, or a few cores, you can usually get what you need, which is an ERPR and HERTUNU (phonetic) assessment.

And there have been a number of studies published with proliferation indices and looking at EGFR. Now, EGFR is going to be problematic because in the not too distant future there are drug targets for that. You might want to look at those.

Of course, the problem is those are amino assays, and the assays aren't standardized, and you can always have the power to come back and check that later. So I think the cores are probably going to be sufficient to really get the data you need.

My problem that I ran into was the size question because really once you get below one centimeter, you start to run into some problems in the adjuvant area. The literature is really very conflicting in that area, and I think incomplete.

I don't think there's a consensus as to whether node negative, less than one centimeter ERPR positive lesions should really be treated. I think that there may be a consensus about ERPR negative lesions. The microarray data and the proteomics data are not ready for prime time, are not going to be ready for prime time for five years. So I would just eliminate that from any regulatory issue.

So in order to deal with that issue, I would simply exclude any mass that's less than one centimeter from such a design because I just don't feel that you will have sufficient data to verify that pathologically without resecting it and, therefore, might compromise your decision on adjuvant approaches.

So those are some of the practice design issues that I came up with.

ACTING CHAIRPERSON McCAULEY: Dr. Miller?

DR. DOYLE: Can I ask him one question?

ACTING CHAIRPERSON McCAULEY: Let's finish the panel comments and then we'll come back to your question.

Dr. Miller.

DR. MILLER: I guess this study is different than, say, when we had to make a decision about whether to do a mastectomy or a lumpectomy, which was like a whole shift in mentality for treating breast cancer. This is just looking at an alternative way to do a lumpectomy, and the main question is: is it complete enough? Does it compare to a surgical lumpectomy in terms of completeness of lumpectomy?

Because all of the other issues about treating patients with lumpectomy and radiation or chemotherapy and their nodal stats and everything, those are in my mind all unchanged. The only question is: does this do an adequate lumpectomy to control the local disease?

So I think a trial which starts to put patients into a group that are treated with this and followed just as we could lumpectomy patients may be modeled after, you know, the NSABP trials to look at lumpectomy would be suitable and just go for as many years as you need to and just treat the patients with this as an alternative.

I feel comfortable with this if I'm convinced that this gets the mass out. Conceptually in my mind I don't see why it would be any different than doing an open lumpectomy.

ACTING CHAIRPERSON McCAULEY: So basically what you're saying is that starting a pivotal trial really is based on the feasibility or based on the success of a feasibility study to demonstrate the accuracy of ablation.

DR. MILLER: That's right.

ACTING CHAIRPERSON McCAULEY: Ms. Brown.

MS. BROWN: I don't have anything to add to the discussion.

ACTING CHAIRPERSON McCAULEY: Dr. Doyle.

DR. DOYLE: Nor do I.

ACTING CHAIRPERSON McCAULEY: Dr. Blumenstein, any further comments?

DR. BLUMENSTEIN: Just a couple more points here. One of the strategies that could be used here is one of accelerated approval. In other words, the ultimate outcome for women being treated with breast cancer is whether they have shortened life as a result of inadequate treatment.

So it seem to me that really the definitive endpoint that one has to discuss is survival, but it's unreasonable to have to wait that long. And so the FDA has come up with a set of regulations called accelerated approval on which there's a conditional approval based on a surrogate for a definitive endpoint.

And in a trial like this, I think that one would probably want to design it with survival as the primary endpoint, but a planned early analysis of recurrence that would take place early on and allow the publication of the results with respect to recurrence, but have the ability to ultimately assess the survival difference in the trial.

And this is sort of a new style that is used under this accelerated approval program. That's all I want to say.

ACTING CHAIRPERSON McCAULEY: Dr. Choti.

DR. CHOTI: I think for such a pivotal trial local recurrence should be the primary endpoint because that's really what we're looking at, as was mentioned, but perhaps survival as a secondary endpoint.

Ideally randomized trial, ideally T1 cancers, lumpectomy versus ablation, all with radiation therapy, with

or without positive nodes, although perhaps chemotherapy may have an impact on local recurrence. That's another question, although maybe all patients if it's over one sonometer will all get chemotherapy.

The problem is as you said. The number, the power is just going to be very hard to do that. I didn't know that 6,300 for ten years is a massive study. Yes, you can take away radiation. Your event rate will go up, but it's unethical.

So I think that whether to stretch the boundaries to larger tumors, the problem with that is that these therapies, at least if you extrapolate from other soft tissue, liver and elsewhere, the local recurrence rate goes up with the size. So that it is a worse ablation. The efficacy of the ablation will go up as the tumor size goes up.

And so to start doing five centimeter tumors, you're going to have 30 percent local recurrence rates and so forth, and it's probably not going to be and it's also not going to be used clinically for large tumors.

So I think that it doesn't make sense to do big tumors. The problem is it's going to need to be a big

trial.

Endpoint local recurrence, assessment, I think standard imaging, perhaps adding some newer imaging modalities, and probably serial biopsies, definitely if there's anything suspicious, and probably some program to assess with, you know, standard biopsies, that would be an option, and then salvage lumpectomy or salvage mastectomy if recurrence occurs.

An alternative to explore is a nonrandomized trial with T1 all radiation and then just compare local recurrence to historic controls. That would be one way to perhaps shorten the number and then just see if you achieve six percent or less local recurrence rate in that setting. Then that could perhaps be a model of proving nonequivalency, and I think the duration needs to be long, five, ten years.

Any other further comments from the panel members? Ms. Brown.

MS. BROWN: Would there be a way to design it so that approval on a pivotal trial could be done after one or two years with the requirement for a long post approval follow-up so that if something emerged later you'd be able

to spot it?

DR. BLUMENSTEIN: That's what I wa talking about in terms of --

MS. BROWN: It's a little different. This would be actually a frank approval after one or two years of follow-up and then a post approval. So I think it's what you were talking about, but I think there is a mechanism in place for FDA to do something like this.

DR. BLUMENSTEIN: Well, I think that under the accelerated approval I think it's called a conditional approval, but it carries all the weight, as I understand it, of a full approval, but you are obliged to do the long-term follow-up on the surrogate endpoint to validate that it was, in fact, a valid endpoint.

And with respect to what you were saying about primary versus secondary, the reason that I when I stated it called the survival endpoint primary is just simply because that you want to size the trial to ultimately know the answer with respect to survival because that's what's important.

To say that there's a planned early analysis with publication of results in submission to the FDA of

local recurrence as an early endpoint, that is in a sense a primary endpoint. It's just that the advantage of a trial of that nature is that you have already set up the mechanism for validating the long-term endpoint, and so the patients are already in the trial. They are already being followed and so forth like that.

So you ultimately get the validation without having to initiate a second trial. And let's just think about that for a minute. If you had to initiate a second trial after a short-term trial on a surrogate endpoint like recurrence, it would be unethical to randomize at that point.

Now, with respect to what you were saying about a single arm trial, everything that I've heard here screams out that there are no reference data for which you could do a single arm trial because every time I turn around people are saying, "Well, you can't do it if the tumor is close to the skin. You can't do it if this, that and the other."

And so there are no reference data that one could fish out of a database to serve as a proper reference group for a single arm trial.

DR. CHOTI: No, I think if you had local

recurrence rates under five, six percent at five, ten years, I think that may be sufficient pivotal data to show that local control is effective. So I don't know.

The other thing, by the way, is that following ablation it may be that local recurrence comes faster than local recurrence following margin negative lumpectomy because failure following ablation may also be or increased failure following ablation may be due to some persistence rather than kind of this multi-focal or small focus that was missed in the margin.

So it may be that if, indeed, the local recurrence rate is higher, some of those may hit earlier and you'll know that quicker than that ten-year duration, but who knows.

DR. BLUMENSTEIN: One more thing on this idea of doing the dual endpoint type of trial is that the criterion for success for the local recurrence doesn't have to be as strict as the criterion for success with respect to survival. In fact, you have a lot of flexibility in how you set that up.

You know, for example, from BO6 and so forth that local recurrences don't matter that much, and so the

criteria for inferiority can be fairly loose because you think, well, it doesn't really make that much difference, but the criterion for survival could be tighter and ultimately assessed.

There's a lot of knobs one would have to turn in making that design, but the real advantage is that ultimately you do get the survival answer.

DR. HALBERG: Can I just make a comment? I think it's very important that when we talk about surrogate endpoints and you talk about local control, that not seeing failure, not seeing a local recurrence does not equal success.

T1 tumors, they may sooner after ablation, but we don't know that. If you look at T1 failures, they occur after five years. So if you don't see follow-up at two years or five years, that really doesn't mean anything.

So I think publishing data, if it is successful, I think it would be important to know that there weren't local recurrences early, but I think that's very different from saying something is successful, and so I would really caution everyone on how that, you know, interim analysis is done and what is generated from that.

And I just wanted to echo back to what Dean was saying about eliminating node positive patients. If you take T1/N1 patients, it's not that they will die before local recurrence. In that setting you see the local recurrence goes faster. You don't actually see particularly more local recurrences because combined with that modality therapy with chemotherapy and radiation therapy after lumpectomy, it's actually quite successful in terms of local control.

But those patients who fail the time course to failure is much earlier, and that's why I was suggesting that might not be an unreasonable group to include.

ACTING CHAIRPERSON McCAULEY: One final comment.

DR. KOPANS: I just want to make one comment on local recurrence, and even though it may be scientifically innocuous for the individual woman who has a local recurrence, it's psychologically very damaging. That may not be, you know, the significant endpoint issue, but it's still something to keep in mind.

ACTING CHAIRPERSON McCAULEY: The last final comment.

DR. BRENNER: Oh, I get it. And that's really

the point here, is that this is a treatment for local recurrence or for local control and that what has come out here is that that's different from systemic control of this disease, and whether you control locally using surgery or you control locally using this modality, it's still a local control measure, and the data to data, at least to my interpretation, do not support the idea that local control does predict survival.

So you could very well end up with a negative survival outcome and yet a positive local control outcome, and that might be sufficient for this modality because what you're really looking at in a funny way is a cosmesis endpoint, hence the need for a validated set of quality of life as well as cosmesis data because that might be the indication for approval here.

ACTING CHAIRPERSON McCAULEY: Dr. Witten, there has been extensive discussion by the panel relative to Question No. 2. Has this information been helpful such that we can move on to Question 3?

DR. WITTEN: Yes. Thank you.

ACTING CHAIRPERSON McCAULEY: Can we have the third question, please?

Radiation therapy and chemotherapy may be concomitantly used in patients who receive tumor ablation or tumor thermal ablation in lieu of lumpectomy. Thermal ablation of cancer may affect the radio or chemosensitivity of the surrounding breast tissue. Please provide recommendations regarding the best way that this concern may be addressed in clinical trials aimed at the understanding, the safety, and effectiveness of thermal ablation for the treatment of breast cancer.

We have two lead panelists for this particular question. We'll first hear from Dr. Brenner and secondarily from Dr. Halberg.

DR. BRENNER: My response to this question was I don't know how to answer it. The reason is that within a clinical design I don't know how you can really get at this question definitively. I think you really would need to go back to the rodent models and clear out cells, get them into primary culture and test the question because this is really a biological question.

And the question can really be divided into two areas. What's the effect of thermal or cryo or approaches to cells at the molecular level? And I don't know how you

can do that in breast human samples, but you can do it perhaps from rodent models, preferably rodent models with carcinogenesis.

Secondarily, an equally important question is what are the effects on the stroma, and the stroma would be both fat as well as fibrous stroma.

And, again, those questions I think are probably best answered biologically in the rodent because I just don't know how I could really answer those questions biologically in humans unless I pulled the tissue out in the prove a principle trial that we responded to in Question 1 and then try to deal with those tissue samples by probing potential mechanisms of thermal injury.

That begs the hypoxia question, which has been discussed in detail here, and since I'm not a radiation oncologist, hypoxia to me was not as relevant because if you're thinking about cytotoxic events or, even better, biological and targeted therapies that are likely to really deal with signal transduction events, for example, UGFR targeters which are on the market now actually; in other words, TK kinds of phosphorylation inhibitors, that's where it's going.

And so, again, I'd want to have the tissue samples prepared in both frozen and fixed manners so that I could then probe those questions in order to try to get such an answer, and then ask the question simply: is there a proliferative effect? Is there an apoptotic effect? And then are there specific phosphorylation or immediate effects from human samples in order to really start to address?

So to me this was a biological question that really related to mechanism of cellular death, so to speak, or cellular ablation or whether these tools cause necrosis or apoptosis. I mean all of those kinds of mechanistic questions that really an oncologist would think about that one would have to test on human tissues.

So it really becomes a collection method and then probing those issues.

Will that affect cytotoxics? I haven't the faintest idea.

Will these affect targeted agents? I don't know.

Will they affect hormonal approaches? Again, I'm not aware of any of these data, and I probed back into the heat data that was published many years ago. The only

data really are about membrane fluidity and dynamics, but not really about pathway mechanisms to the best of my knowledge.

Perhaps people in the audience might have some more recent biological information.

In terms of hypoxia, I'll leave that to the radiation oncologists.

ACTING CHAIRPERSON McCAULEY: Dr. Halberg.

DR. HALBERG: Again, many of the issues have already been brought up. I thought what I might do is just read the first paragraph in the editorial in last week's International Journal of Radiation Oncology, Biology and Physics, which is the main radiation oncology journal, and there was an editorial by Arian Begg, who is one of the preeminent hypoxia researchers, and it is actually looking at different hypoxia markers.

And I think that if I just read what he writes, it basically summarizes the issues quite eloquently.

"It is now abundantly clear that tumor hypoxia is a strong prognostic factor for outcome in many forms of cancer. High tumor hypoxia is associated with a poor outcome after treatment with any of the major treatment

modalities: surgery, radiation therapy, and chemotherapy.

"For radiotherapy, an obvious contributing factor will be intrinsic radioresistance of hypoxic cells, a phenomenon known and well studied since the first half of the last century.

"For chemotherapy, contributing factors are reduced to drug delivery hypoxic cells, and for psychodependent drugs, the reduced proliferation rate of hypoxic cells.

"In more recent years, hypoxia has also been shown to influence the invasive and metastatic properties of tumor cells and to lead to the selection of apoptotic resistance cells resulting in a more malignant phenotype. This will affect outcome after all treatment forms, including surgery."

And he goes on to say at the beginning of the next paragraph, "Eliminating hypoxic cells is, therefore, a very useful therapeutic goal."

And we have just heard from the presenters that we're knowingly generating a hypoxic zone around the tumor, around the area of coagulative necrosis. It doesn't matter if it's laser or cryo or any of the other forms of thermal

ablation. You are cutting off blood supply in the area of the tumor, and by definition you're perturbing the environment right around that, and by definition you're creating hypoxia, and it's well established that hypoxia increases radiation resistance.

And so I think this is an issue that we have to keep in mind.

I just thought I would also read there is actually data emerging in the animal models on hypoxia, and both chemo sensitivity and mutagenesis. I thought I would -- a group at Yale is very active in investigating this in animal models, and I thought I'd read the last sentence of a recent article that they published as well.

"The concept that the conditions of the tumor microenvironment can inhibit DNA repair and consequently promote genetic instability provides the basis for understanding the observation that very hypoxic tumors follow a more aggressive clinical course."

So that sort of summarizes my main concerns around hypoxia. With that in mind, I tried to investigate if there are ways that we can measure hypoxia if you've done ablation and you're not going to perform a lumpectomy.

As I've already mentioned, you can give patients pimonidazole, a low dose of it, the day before lumpectomy and assess for hypoxia in the resected tissue if you do a lumpectomy.

If you do not do a lumpectomy, I tried to see if there were any imaging modalities that might be useful in terms of assessing hypoxia, and there are none that are ready for prime time.

The group at M.D. Anderson has looked at a compound called copper ATSM and are actively studying that with PET, and apparently that defines a five millimeter rim of hypoxia quite well, and so one might in a very limited way ask that investigators there be funded to look at the copper ATSM plus PET in these patients who have undergone I guess M.D. Anderson is radio frequency ablation.

ACTING CHAIRPERSON McCAULEY: Dr. Kopans.

DR. KOPANS: Two comments. One in support of what was just said. I think you can look at the hypoxia, and the only way you're going to know what its effect, I mean, we know that hypoxia does decrease radio sensitivity, but you really don't know for sure until you do a human study as to how significant that's going to be.

The other point about chemotherapy, I'm not actually sure that chemotherapy is that important in terms of local control, but in our patients where we're doing neoadjuvant chemotherapy now, we're seeing some very strange patterns of response.

One of the unusual patterns is that you have the diameter of the tumor remains the same, but you have islands of residual tumor in this ghost zone of the previous tumor, and you know, the question is: does this have to do with the local vascularity of the tumor and that the chemotherapeutic agents are not getting to those zones?

I mean it's open for speculation. So I'm not sure it's completely unimportant in terms of the benefits of chemotherapy to again have vascular damage the consequences of which we don't really fully understand.

ACTING CHAIRPERSON McCAULEY: Dr. Miller.

DR. MILLER: I don't have anything to add.

ACTING CHAIRPERSON McCAULEY: Ms. Brown.

MS. BROWN: I have nothing to add.

ACTING CHAIRPERSON McCAULEY: Dr. Doyle?

DR. DOYLE: Nor I.

ACTING CHAIRPERSON McCAULEY: Dr. Blumenstein?

DR. BLUMENSTEIN: Well, I think that the at least theoretical possibility just screams out that ultimately you have to know something about survival.

ACTING CHAIRPERSON McCAULEY: Dr. Choti.

DR. CHOTI: A couple of comments. First, it's not necessarily that clear that ablation causes hypoxia. So I think that does have to be studied. In fact, in liver tumors and other things, we don't know about hypoxia, but certainly the rim is hyperemic and hypermetabolic on PET, and so it may be that it's enhancing at least blood flow in the area of the zone that's not totally necrotic.

So it's hard to know what exactly is happening in that microenvironment immediately adjacent to the dead cells. Interesting to study in the breast, and it may be different than the liver, for example.

I think ultimately though the best way to address it in a clinical trial, address the impact on chemo and radiation therapy, will be the same endpoints that we're looking at: local control and survival.

And I think if it's impacted in a deleterious way, then that will give us some clues to that.

ACTING CHAIRPERSON McCAULEY: Dr. Leitch.

DR. LEITCH: I don't have too much to add other than to say we do need to evaluate whether or not the hypoxia occurs and figure out some techniques to do that, and the endpoints I think also ultimately are going to be does it make a difference, and that's what you will see in the outcomes.

ACTING CHAIRPERSON McCAULEY: Dr. Lanzafame, please.

DR. LANZAFAME: Being a somewhat simple surgeon, I would just suggest that we handle these patients as we would handle a lumpectomy patient so that if the patient would as standard of care receive radiation and/or chemotherapy or both, that the same patient population do that. We may have to control that a little bit in the trial because there's some variations on the theme in terms of centers and parts of the country, but I think nonetheless those are issues that could be nailed down.

The issue of local hypoxia duration, et cetera, again, very scientifically interesting. I think we also have to understand that when we physically remove a tumor with lumpectomy and then do radiation, there's a specific time course over which the radiation therapist doesn't

deliver radiation therapy, which is really empiric based on information in the really good old days about what people thought about wounds and wound healing.

So I'm not sure that we really have an adequate understanding of what we're doing when we surgically excise wounds and how we sequence our events, but just like we were starting to do with multi-nodal chemotherapy, we're beginning to understand some of those things, and I think some of the issues, the point have been raised. They're very good, but I don't think they're an isolated event relative to these technologies.

They really interface a lot of what we're handling clinically.

ACTING CHAIRPERSON McCAULEY: Dr. LoCicero.

DR. LoCICERO: Just to expand on that a little bit, lest we get hung up only on hypoxia, the ablative therapy will produce a dense scar, and this may alter the radiation physics locally.

Now radiation is sort of like horseshoes, only it's a large horseshoe. So you only need to be close maybe, but I think the endpoints will remain the same, but I don't know that the sponsor can address only the hypoxia issue as

a side study.

ACTING CHAIRPERSON McCAULEY: Dr. Solomon.

DR. SOLOMON: When one makes an ablation injury there's increased blood flow to the area of the injury and pretty consistently you can see that there's a rim of hyperemia around the lesion. We and others in the literature have shown that there can be increased drug delivery to that area, the margin. That happens to be the area where, you know, it's on the margin, and that may be where the recurrence or the failed treatment is.

So in some ways you might find that the increased blood flow enhances chemotherapy or radiation therapy, for that matter, and so it's an unknown. I think the endpoints that have been discussed will follow it.

The other issue that hasn't really been discussed right now is just again for targeting the lesion, you need to have good imaging, a defined lesion, and chemotherapy and radiation may alter the ability to -- the conspicuity of the lesion, and so that might be something to think about avoiding prior to the procedure, as mentioned in several of the articles provided.

ACTING CHAIRPERSON McCAULEY: Any other comments

from the panel?

(No response.)

ACTING CHAIRPERSON McCAULEY: Dr. Witten, does that satisfy answers to Question No. 3?

DR. WITTEN: Yes, thank you.

ACTING CHAIRPERSON McCAULEY: We'll move on to Question No. 4

Neoadjuvant and adjuvant chemotherapy or radiation therapy may affect the ability to radiographically visualize the tumor margins either at the time of thermal ablation or during follow-up for recurrence. Please discuss how limitations of radiographic visualization will affect the selection of candidates for these procedures and make recommendations regarding appropriate follow-up of these patients.

Dr. Kopans will be the lead discusser for this question.

DR. KOPANS: Well, i think certainly at the beginning it probably would not be advisable to enter patients into a trial unless you -- it would have to be a separate trial from what we've already discussed certainly. There's no question that neoadjuvant chemotherapy alters the

imaging appearance of tumors. As many as 30 percent of invasive cancers may disappear completely on imaging, and the problem would be certainly from a noninvasive ablative technique what to aim at.

We try to position radio opaque and ultrasound visible clips in the tumor prior to neoadjuvant therapy. The accuracy of that placement can be variable. With a surgical excision following neoadjuvant therapy there is, I think, because of the volume of tissue that's removed the likelihood of excising the tumor even if the clip hasn't been placed precisely. It's probably okay. We don't know for sure.

I would be concerned with a precise targeting technique, such as the ablative techniques that we've been talking about, that the precision may actually work against actually hitting where the tumor had been.

In addition, as I mentioned already, tumors respond to neoadjuvant therapy in a multiplicity of ways. One of them is that they break up, as I said, or the residual tumor is in scattered islands of tissue. So targeting that may be difficult, again, for an ablative procedure.

So I think that we still are really at the beginning of understanding the effects of neoadjuvant therapy. Again, imaging, as I've said repeatedly and others have also said, is not certainly microscopically accurate in the pristine tumor. Once the tumor has had other effects on it, it becomes even harder to image.

Ultrasound lesions can be very difficult to image once they've been treated with neoadjuvant chemotherapy, mammography, and magnetic resonance. All of the imaging tests that are being looked at have a variable effect from neoadjuvant, but certainly make it harder to see them.

ACTING CHAIRPERSON McCAULEY: Any comments, Dr. Witten, at this point?

DR. WITTEN: No.

ACTING CHAIRPERSON McCAULEY: Okay. Dr. Halberg, any further comments?

DR. HALBERG: No.

ACTING CHAIRPERSON McCAULEY: Dr. Solomon?

DR. SOLOMON: No.

ACTING CHAIRPERSON McCAULEY: Dr. LoCicero?

DR. LoCICERO: No, no comments.

ACTING CHAIRPERSON McCAULEY: Dr. Lanzafame?

DR. LANZAFAME: No.

ACTING CHAIRPERSON McCAULEY: Dr. Leitch?

DR. LEITCH: No.

ACTING CHAIRPERSON McCAULEY: Dr. Choti?

DR. CHOTI: A couple of comments. One is one of my biggest concerns just coming into this is what the postoperative imaging of these ablation zones will be and whether the ability to detect a recurrence will be diminished compared to lumpectomy.

Again, in ablation of other sites, this is a big problem. That is, following an ablation zone to see whether recurrence occurs. In breast it's different because actually the lumpectomy causes a big zone that obscures the ability to detect recurrence, different than other sites.

So it may be very similar. You're just going to see this big area, and you're just going to have to try to determine whether a recurrence is occurring in that area. But this is a problem as far as imaging.

Regarding adjuvant therapy, clearly postoperative radiation therapy impacts on the ability to detect recurrence, but again, it's similar to lumpectomy.

Certainly that's the way it's going to be done clinically. So it's going to be an ablation plus radiation and recurrence assessment has to be done in the face of adjuvant therapy.

ACTING CHAIRPERSON McCAULEY: Dr. Blumenstein.

DR. BLUMENSTEIN: No further comment.

ACTING CHAIRPERSON McCAULEY: Dr. Doyle.

DR. DOYLE: No comment.

ACTING CHAIRPERSON McCAULEY: Ms. Brown.

MS. BROWN: No comment.

ACTING CHAIRPERSON McCAULEY: Dr. Miller.

DR. MILLER: At M.D. Anderson in the trial of the radio frequency ablation the only failure that was -- in 20 patients, the only failure was one who had preoperative chemotherapy in a lesion that was four centimeters that was reduced to a centimeter and a half, and when they did the ablation, it was complete ablation of the tumor, but there were foci of tumor in that four centimeter original volume of tissue that was not imaged after the neoadjuvant chemotherapy.

So I think that, you know, the patients who get neoadjuvant therapy should be excluded from the trial and

just emphasizes that patients should be selected for these trials who have very discrete tumors, that there's good confidence that the imaging is telling you exactly where the tumor is.

ACTING CHAIRPERSON McCAULEY: Dr. Brenner.

DR. BRENNER: I have no comment.

ACTING CHAIRPERSON McCAULEY: Dr. Kopans, any comment relative to Dr. Miller?

DR. KOPANS: Comments on my comment. I think the issue of recognizing recurrences, the point were well taken. I would only point out that our experience with recurrence following lumpectomy and radiation in the modern era is incredibly small because we don't see a lot of recurrences anymore.

So you know, I think these recurrences will probably look like an increase in density on an X-ray and an increase in hypo code (phonetic) tissue on an ultrasound, but we really don't know. That's a good point.

But I do think that serial biopsies should be considered at least in the pivotal trial, and I think exploring imaging modalities of PET, you know, diffusion MR and other kinds f things, I think, looking at the periphery

extremely carefully to try to -- of these ablation zones will be important biologic endpoints that will be helpful.

ACTING CHAIRPERSON McCAULEY: Dr. Witten, you had a comment?

DR. WITTEN: I had a question of Dr. Choti, but it's been answered.

ACTING CHAIRPERSON McCAULEY: Any further discussion from panel members?

(No response.)

ACTING CHAIRPERSON McCAULEY: Have the comments been sufficient to answer Question No. 4?

DR. WITTEN: Yes.

ACTING CHAIRPERSON McCAULEY: Are there any comments or concluding remarks from any of the panel members?

MS. BROWN: I have one comment.

ACTING CHAIRPERSON McCAULEY: Ms. Brown.

MS. BROWN: As a member of industry when I hear the possibility that studies might be thousands of patients and follow-up might be ten years or five years, it's a signal that companies may not be able to develop technologies like this because that's very expensive.

So there's a balancing act that's going on here with respect to will these things come to market if that's what it takes.

ACTING CHAIRPERSON McCAULEY: Dr. Blumenstein?

DR. BLUMENSTEIN: Yeah, I've been concerned about this as well, and I think that one of the possible solutions is sort of an interagency cooperation whereby in this case perhaps some of the National Cancer Institute funded cooperative groups could be a basis of doing studies of the nature that we're talking about here.

We've already talked about NSABP and the American College of Surgeons' Oncology Group and Radiation Therapy Oncology Group and so forth like that. These are well funded infrastructures that do trials quite efficiently with respect to costs and so forth, and I think that we just really haven't exploited these things.

I'm a refugee of that system, and I think that it's a national resource, and that national resource isn't being exploited to the degree that it could by industry and the FDA and the NCI.

DR. KOPANS: There actually is a model for that with the DMIS study that's going on now looking at digital

mammography compared to film screen mammography where FDA has approved digital mammography, but there is now a post approval study going on.

Initially it was going to be mandated by FDA. Now it's just happening because the money was earmarked, but it seems to me you could do I think you mentioned or it was mentioned earlier an approval with the requirement of maintaining follow-up studies over time.

ACTING CHAIRPERSON McCAULEY: Dr. Choti, you had a comment?

DR. CHOTI: No.

ACTING CHAIRPERSON McCAULEY: Dr. Leitch?

DR. LEITCH: I think for industry the other thing is identifying a big problem that this can fix as opposed to a small problem where there's less of a fix that it gives.

So like I said, the hard situations where you'd like to do breast preservation, but it prevents a difficult circumstance because of size of the tumor, you know, lobular, whatever you want to say, all of the things that make preservation difficult for those patients who really desire it; if you had a technique that would facilitate

preservation in patients, then to me that's an easier thing to get through than this kind of thing where, you know, you require these sort of dramatic, big trials, you know, to get to the endpoint.

ACTING CHAIRPERSON McCAULEY: Dr. Brenner?

DR. BRENNER: I guess I'd like to assure industry that, indeed, at least I was very sensitive to that issue and tried to grapple with the issue of a surrogate in order to avoid such a huge cohort. The problem you run into here is the already high level success of the state of the art, and then that forces an equivalence design on you.

And once you're there, then you're stuck. You're stuck with large cohorts whether you like it or not because Brent won't let you prove it otherwise.

(Laughter.)

DR. BRENNER: It's all his fault. You blame it on the biostatistician.

But I mean, getting at truth is really difficult in an area where you already have outstanding result. And one possible work-around was what I think we've been alluding to, was to attempt a quality of life with a cosmesis endpoint as a standard for an interim approval a la

Brent's design.

As a potential, quote, superiority endpoint, that might allow you perhaps to write your trial with less size than you would need otherwise, but I think we were certainly very sensitive to that, but kind of boxed in with the state of the art, and that's unfortunate for you, but it's great for the patients in that there is good local control.

ACTING CHAIRPERSON McCAULEY: Any other comments?

DR. MILLER: Can I make one more? I hate to prolong this, but if I just could make one more.

You know, there's some ways -- and I may be naive about this. I apologize if that's true -- but in some ways this is like asking is it better to use a Barr Parker scalpel or a scalpel from another company to do a lumpectomy and designing a giant clinical trial which will determine whether survival is superior using one of those two ways to ablate the tumor.

I mean, the primary issue here, it's not a fundamental change in how we're treating the breast. It's just a different way to ablate the tumor, and I think if we

focus on are we getting adequate tumor ablation locally with this method, that answers the major question, and then all of the other questions of survival I don't think we have to withhold sort of endorsing this approach pending confirmation in ten to 15 years whether it's equivalent survival unless we can really come up with a real rational reason why we can suspect fundamentally change the way the tumor behaves if we play it like this.

DR. HALBERG: Well, I think that when you lose margin assessment, I mean, I'm sure in the investigator's hands here that they will get, you know, incredible local control. I'm not so sure when a technology is generalized that that can always be said.

It took a long time to establish that, you know, even a small degree of positive margins increases local recurrence risk, and I feel like our primary obligation is to our women with breast cancer, the majority of whom get excellent cosmesis with a lumpectomy, and there are going to be a large number of patients who have the potential to have residual tumor that's not ablated.

I'm playing a little bit of devil's advocate here, but I think it's important to keep that in mind.

ACTING CHAIRPERSON McCAULEY: Dr. Doyle?

DR. DOYLE: I think listening with my consumer rep. hat on I've heard a great deal today about some of the possible risks, but I've heard less about the benefits, and cosmesis seeming to be the one.

And I was very impressed with something that Dr. Lanzafame said, that I think it is different. When you ablate something and take it out, it's different from killing it and leaving it in. I think there is a difference in what you're talking about.

ACTING CHAIRPERSON McCAULEY: Other comments from panel members?

(No response.)

ACTING CHAIRPERSON McCAULEY: Well, I'd like to thank the panel for their very fruitful discussion, and I'm sure it's very helpful to the FDA. This meeting is now adjourned.

DR. KRAUSE: Just one quick comment. If anybody wants to keep the materials from this meeting, they're certainly welcome to. There's nothing confidential here. Anything you want to throw away just leave on the table and it will get picked up.

Thank you.

(Whereupon, at 4:23 p.m., the meeting was concluded.)