

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

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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

	<u>PAGE</u>
Deputization of Temporary Voting Member.....	7
Conflict of Interest Statement	8
Panel Introduction	11
Update Since Last Meeting, Stephen P. Rhodes ..	14
<u>Reclassification of Absorbable Hemostatic</u>	
<u>Agents and Dressings:</u>	
Industry Presentation:	
John D. Paulson, Ph.D.	19
Lene Retboll Muller	35
Judith E. O'Grady, R.N.	43
FDA Presentation:	
David Krause, Ph.D.	54
Panel Deliberations and Address FDA Questions .	76
Reclassification Questionnaire and Vote	107
Presentation of Dr. Keyvan Farahani	158
Panel Introduction	161
Open Public Comment	165
<u>Clinical Issues in Regards to Medical Devices</u>	
<u>for the Ablation of Breast Tumors:</u>	
FDA Presentation:	
Binita S. Ashar, M.D.	166
Industry Presentation, Kelsey, Inc.:	
George M. Burditt	173
Open Panel Discussions and FDA Questions	209

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 spectral 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 of surgical and spongostinal (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 due 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, suture 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 enclosed 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 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? Are 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 since 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 image 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 consumer 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.