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MEDICAL DEVICES ADVISORY COMMITTEE

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Meeting of:

GENERAL AND PLASTIC

SURGERY DEVICES PANEL

OPEN SESSION

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## **APPEARANCES**

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P R O C E E D I N G S

(9:53 a.m.)

**AGENDA ITEM: Conflict of Interest and Opening****Remarks.**

MR. DEMIAN: We are ready to begin this meeting of the General and Plastic Surgery Devices Panel. I am the acting executive director of this meeting and the executive secretary for the Orthopedics and Rehabilitation Devices Panel.

I would like to remind everyone that you are requested to sign in on the attendance sheets, which are available on the tables by the door.

You may also pick up an agenda, panel meeting roster, and information about today's meeting there.

The information includes how to find out about future meeting dates through the advisory panel phone line, and also obtain meeting minutes or transcripts.

This and other panel meeting information, including panel meeting summaries, is now available on the world wide web.

Advisory panel meeting activities are described in the general information folder listed on the CDRH home page.

Before turning this meeting over to Dr. Morrow, I will read the conflict of interest statement into the record.

The following announcement addresses the conflict of

interest issues associated with the meeting, and it is part of the record to preclude even the appearance of any impropriety.

To determine if any conflict existed, the agency reviewed the submitted agenda, 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 employers' financial interests.

However, the agency has determined that participation of serving members and consultants in the meeting, and the produced services outweigh the potential conflict of interest involved, is in the best interests of the government.

We would like to note for the record that the agency took into consideration certain matters regarding Drs. Joseph Boykin and Susan Galandiuk.

These individuals reported interests in funds at issue or matters not relating to today's deliberations.

Since these interests are not related to the specific issues before the panel, the agency has determined that they may participate fully today.

In the event that today's discussions involve any other products or funds not already on the agenda, for which

FDA participants have a financial interest, the participant 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 interests of fairness, that all persons making statements or a presentation disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

At this time, I would like to turn the meeting over to our chairperson, Dr. Monica Morrow.

DR. MORROW: Good morning. I am Monica Morrow, the chair of the general and plastic surgery devices panel.

Today, the panel will be making recommendations to the FDA over classification of five wound dressing categories and the classification of topical oxygen chambers for extremities.

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

Before we begin the meeting, I would like to ask our distinguished panel members, who are generously giving their time to help the FDA in the matters being discussed today, as well as the other FDA staff seated at this table, to introduce themselves.

Please state your name, affiliation and your position and your area of expertise. Dr. Chang, we will start over there.

DR. CHANG: I am Phyllis Chang, associate professor, department of surgery, section on plastic surgery, the University of Iowa in Iowa City, Iowa.

DR. BOYKIN: Dr. Joseph Boykin, a plastic surgeon from Richmond, Virginia. I am the medical director of the Columbia Wound Healing Center, and assistant professor of plastic surgery at the Medical College of Virginia.

DR. WHELAN: Tom Whelan. I am associate professor of surgery in pediatrics at Robert Wood Johnson Medical School and head of their division of pediatric surgery in Camden.

DR. BURNS: I am Jim Burns, vice president of biomaterials and surgical parts research at Genzyme. I am the industry rep for this panel, a non-voting representative.

MS. BROWN DAVIS: Good morning. I am Carolyn Brown Davis. I am the executive director of the Breast Cancer Resource Committee, an advocacy group for African American women. I am a consumer rep, non-voting, temporary consumer rep.

DR. WITTEN: Celia Witten, division director, PGRP at ODP at FDA.

DR. ANDERSON: Ben Anderson, associate professor of

surgery, University of Washington, Seattle. My expertise is breast surgery. I am the director of the breast program there.

DR. GALANDIUK: Susan Galandiuk. I am a colo-rectal surgeon and associate professor of surgery at the University of Louisville, in Louisville, Kentucky.

DR. MORROW: I am Monica Morrow, professor of surgery, director of clinical breast programs at Northwestern University.

Before we begin the wound dressing portion of the hearing, we will have Mr. Stephen Rhodes, who is the branch chief of the plastic and reconstructive surgery devices branch, give us an update of activities from the last few meetings.

**AGENDA ITEM: Update Since the Last Meeting.**

MR. RHODES: The FDA approved two of the products that we discussed in the January panel meeting, since we met.

The first product is Abra-graft(?), from Organogenesis, Incorporated. It is a cellular wound dressing product for venous insufficiency in ulcers. That was approved in May of this year.

The second product is Dermabond from Columbia Medical. That is a tissue product for holding close opposed edges of wounds caused by lacerations in surgical procedures.

That product was approved in August of this year. Thank you.

DR. MORROW: Thank you, Mr. Rhodes. Next we will hear from Mr. Neil Ogden, also from the general surgery devices branch, who will give us an update on the year 2000 computer issues.

**AGENDA ITEM: Year 2000 Information.**

MR. OGDEN: Thank you, Dr. Morrow. I have been asked to give this presentation on behalf of the agency, to increase public awareness of the Year 2000 date problem in computer software and medical devices.

Digital doomsday? A medical device problem, health care problem, millennium bug syndrome.

From 1996, we have upwards of 80 percent of existing PCs are unreliable. Many medical devices utilize PCs for operational control, pacemaker controllers, central monitoring stations, clinical lab instruments.

The largest computer initiative in history needs to begin today, in 1996. One second after, more than 25,000 health care systems will not be working properly.

Medical devices are subject to year 2000 problems: Microprocessor or PC controlled products, software applications, device interfaces to databases and record keeping systems, embedded chips for date display or recording.

What is the year 2000 problem? It is the failure of

computer systems to properly process or display dates, due to representing the year using only two digits or other date-related problems such as failure to recognize a leap year.

An example is 00 leads to confusion between the year 2000 and 1900.

Definition of Year 2000 compliance. For the purposes of the database, year 2000 compliant means, with respect to medical devices and scientific laboratory equipment, that:

The product accurately processes and stores date/time data, including, but not limited to, calculating, comparing, displaying, recording and sequencing operations involving date/time data during, from, into and between the twentieth and twenty-first centuries, and the years 1999 and 2000, including correct processing of leap year data.

Request of the panel? Provide advice regarding problematic devices from the panel's domain of expertise.

Identify types of device which, because of their use of dates, could present risks to patients if not addressed.

Suggestions to CDRH regarding actions to reduce risks from the year 2000 problems.

The address of the FDA product database is [www.fda.gov](http://www.fda.gov). Select the year 2000 item.

FDA/CDRH activities include letters to

manufacturers, guidance to manufacturers, established database of product information on the internet, monitoring and assessment activities, educational activities for manufacturers, clinicians and the public.

Contacts for the year 2000 comments or concerns should be directed to Mr. Tom B. Shope, division of electronics and computer science, Office of Science and Technology in CDRH. There is his e mail address, phone number, or you can contact your panel executive secretary.

In the interests of time, I think I will stop right there. We are running a little late. The panel packs include a complete copy of the slides.

It goes on to detail the exact letters we sent out, when we sent them out and some of the other activities the agency is engaged in to deal with this problem.

It is a serious concern and we would like everyone to be aware of it and to participate in preventing catastrophes from it. Thank you.

DR. MORROW: Thank you, Mr. Ogden. Next, we are going to have an introduction to the classification process of medical devices by Mr. Jim Dillard.

**AGENDA ITEM: Introduction to Classification  
Deliberations for Wound Dressings and for Topical Oxygen  
Chambers for Extremities.**

MR. DILLARD: Thank you, Dr. Morrow. Again, good morning. Thank you, in addition to our thanking the panel members for their participation, I would like to take this opportunity to thank the various organizations and individuals who will also be giving some presentations today, in the interests of both classification of wound care products and reclassification of topical hyperbaric oxygen.

What I would like to do, in addition to the training you received on classification and reclassification, give you a few other pieces of terminology that I think might be used today, so that you get a general understanding and the various public, if they are here, also get an understanding of what we are trying to do today, as well as talk about a few of the specifics regarding the two product types that you will be discussing today.

By way of introduction, I would like to give you just a little bit of a background of classification and reclassification.

I am going to save some of the specifics. Gail Gantt, who is a reviewer in our plastic and reconstructive surgery devices branch, as well as Dr. Chuck Durfer, will be giving you some of the specifics both this morning and this afternoon, about the history of these products and what panel involvement there has been.

I would like to try to be a little bit preemptive and describe why the advisory committee needs to be involved, to give you a sense of both the classification and the reclassification process, the importance of your commitment and involvement.

I will talk a little bit about the process and then answer any questions, and I will also be available throughout the day, if any questions arise about the process.

The definition of a medical device -- just so everybody is on the same page -- in 21 CFR -- actually, this is in the law, in 201(H), it talks about a medical device.

A medical device, as you can see, is intended in the diagnosis, cure, mitigation, treatment or prevention of a disease or a condition. This is also the definition of a drug.

Really, the device separates itself because it does not achieve its intended use through chemical action, and it is not primarily metabolized, although we all know there is a growing need in combination kinds of products, and the lines have been a little bit obscured.

One of the rules of thumb -- this actually is not in the act, but is something I put on my slides. When you think about a device, really it is the physical article that is the product, plus what the device is intended to be used for.

That really is what constitutes a device.

Classification, you heard about this this morning. I am not going to go into too much detail.

Class I devices, the general controls are sufficient to provide reasonable assurance of safety and effectiveness.

Class II, you need additional special controls. Class III, we say that the product cannot be controlled by Class I and Class II controls, and therefore needs premarket approval application.

Congress, again, said that we needed to classify all the medical devices, and it needs to be based on knowledge about their performance.

One of the key pieces, of course, is that Congress said, please classify devices in the lowest regulatory class that provides reasonable assurance that the device is safe and effective.

I think in the act it gives us the opportunity to do that in both classification and reclassification.

Reclassification, just by way of point, can be up or down. Congress did give us the opportunity to do that.

One of the things, and really the primary reason that you all are here today, is that the advisory committees, by statute, need to be involved in original classification, and most of the reclassification efforts that we have.

So, it is one of those things that is statutorily mandated, one of the reasons that we enjoy seeing you all and want to have your recommendations.

It really does provide for public comment, and gives the public also an opportunity, not only in front of you, but through our rule-making process, to comment on our classification efforts.

The other point, really, on this slide that I wanted to highlight, are those transitional devices. That is not a device type that we are talking about here today, but it is another type of device that we will probably be bringing before you.

We do have some transitional devices in both the plastic and the general surgery area.

A transitional device, unlike the two types of devices that we are talking about today, is a product that was previously on the market, but regulated by our Center for Drug Evaluation and Research when the medical device amendments of 1976 came along.

Actually, those products currently need a PMA before they go to market, not a 510(k), but there are quite a few of those. One example of that is hemostatic agents, certainly, in this area.

Class I, you can see kind of a distribution of

devices, class I, class II or class III. Most of our products are class II.

That number of 10 percent in the class III device type will slowly be shrinking to zero in terms of those pre-amendment class III devices.

We are currently working toward having all of our devices very clearly delineated as either class I, predominantly being exempt, class II products that require premarket notification, and class III products being only those products that require either a PMA or a PEP prior to market.

So, some of our efforts -- and that certainly concerns the product this afternoon, which is a class III pre-amendments device, that is why we will be bringing that product, as well as other products, before our panel, to see if there is a recommendation for reclassification.

You have heard about really the three major statutory changes that went into effect, that affected us, at least, in devices with the most recent Food and Drug Modernization Act.

All three of them certainly made the commitment for the lowest class, to provide reasonable assurance of safety and effectiveness.

Really, starting in 1990, Congress pushed pretty

hard and said we really need to take care of all those either unclassified pre-amendments devices, you need to classify all those devices, and you really need to deal with all those class III pre-amendments devices, which we are currently looking at under 510(k).

We need to call for PMAs, we need to reclassify those devices. So, some of this is housecleaning, and I think we will be doing some of that. I think we need to have the device program pretty well squared away so that it is a little less confusing as we advance.

I would like to differentiate a little bit, because some of this is terminology, but there is a much different regulatory meaning to it, the difference between what is meant by a pre-amendments unclassified device, which is the wound care product area that we will be considering this morning, from what a pre-amendments class III device is, the hyperbaric oxygen, the topical hyperbaric oxygen that you will be dealing with this afternoon.

Unclassified pre-amendments, unclassified means that it was marked prior to May 28, 1976, it was on the market, but we never either -- for whatever reason it might have been -- it never got presented to a classification panel, those panels that were put together in the late 1970s to help us classify all medical devices.

All of these products currently can be reviewed under premarket notification. They do not have to submit a premarket approval application for clearance prior to going to market.

As I said, this is sort of the category of wound care products that you are considering today, are in that.

Pre-amendment class III devices are a little bit different. They did go to a panel. A panel did give a recommendation.

The recommendation from a panel could have been different from what the agency actually finally classified the device as.

Chuck will go into some detail about what past panel recommendations were in the topical hyperbaric area, and then what our final determination was.

They currently do require a 510(k) premarket notification for those products that are class III pre-amendment devices, prior to going to marketing.

So, the regulatory requirements currently, as they stand, don't appear, from the premarket standpoint, to be any different for an unclassified device than a class III device.

Actually, that does seem to be a little bit odd, a little bit of a disconnect, which is why we are trying to go through this process, to make sure that we have got products

in the right classification categories, so that they are ready when appropriate.

The only other point that I wanted to make -- and Chuck will go into a little bit more detail -- we could have said in the past, for class III pre-amendment devices, that there was either a safety risk associated with the product, or a safety issue that hadn't been completely addressed.

That might have been an issue, why we said it needs to be a class III device rather than a class II device. Or it could have been for lack of effectiveness information.

Either one of those two or both of them could have been reasons why we said in the end, when we were trying to classify the device, that it should be a class III device as opposed to a class II device.

I think that in the topical hyperbaric area, we will find that it was predominantly a lack of effectiveness information that really caused us to come to a final agency determination of class III back in the middle 1980s.

You also remember the terminology that I think you have seen in your packets, the 515(i), and what does that mean.

The 515(i), that part of the statute talks about the agency's ability to call for information when we think there might be more known about a product than we have at our

disposal.

That, in fact, is what we did for a large portion of the class III pre-amendments devices, and was done for the topical hyperbaric oxygen.

What that, in effect, is asking for is that manufacturers and any interested parties that have information and have data on the product types, to submit it to the agency for consideration for reclassification.

The whole idea is that we would be calling for information to see if there wasn't enough information to actually reclassify the product. You have some of that in your package that we provided to you.

So, why are we asking you to be here? If you haven't garnered some of this from what I already talked about, the predominant reason, I think, in both these areas is that we really do need panel involvement, either statutorily or for your expertise in the area, where really the information is not definitive one way or the other. I think we need a little of each of these in this case.

You will hear from Chuck that wound care products have been before a couple of other advisory committees. Especially Dr. Morrow may be sitting there saying, why do I have to see this again.

I think the reason really is that we have been

working under the premises of the last couple of panel recommendations of how to even look at and separate wound care products.

I think what we need to do now is really ask for a formal recommendation about classification. We are only going to talk about five of those.

There are more than that, so there will be more perhaps in another panel meeting, but they are the much more complex ones. I think the ones we are doing today are the ones that are not at the complex end of the scale.

The other point, of course, for both of these is that it does provide for the open public discussion, which is crucial.

Certainly it is crucial based on FDAMA and Congress' intent for us to really have an open, involved process with all the people who could be affected by regulatory types of decisions.

Today's meeting, as I said, you will see that we are only tackling five types today. We are going to break those up and have you go through each one of the five and give recommendations on classification for each of the five.

I think you will find, as the day goes on, the first one, perhaps, will be much more difficult in terms of the process, but they will get easier, I hope, as you are working

through it.

Again, remember that the recommendation should be based on what the physical description is of the device, and also consider the intended use.

Topical hyperbaric oxygen, I think a point here worth noting is that one of the reasons we asked you to sit down and discuss this is that we do need to consider all known information, and we certainly need to keep at the forefront of our mind what the definition is of valid scientific evidence, and consider all reasonable and valid scientific evidence in a recommendation for reclassification.

Just by way of process for today, as well as what happens once you give your recommendations, today you are going to hear from FDA, who has reviewed, at least from our standpoint, the material that we have available to use.

You are also going to hear from other industry types of groups or individuals, who are concerned about both of these areas.

We certainly are asking you to have open committee discussion and deliberation on issues, about information that is not only in your packets, but what might be presented today, and give a recommendation on classification and reclassification.

Following this panel meeting, we will propose, after

we take into consideration the comments that you make to us and your recommendation to us, we will propose a classification for the products, invite another set of public comment.

We will consider those comments, and then we will issue a final classification regulation, which will include the regulatory requirements.

With that, I think I will close. If there are any questions, certainly I am available now, or at any time during the day. Thank you.

DR. MORROW: Thank you for that very lucid introduction, Mr. Dillard. We will now proceed with the first open public session of the morning.

I would ask that all persons addressing the panel come forward, speak clearly into the microphone, since the transcriptionist is dependent on this means of providing an accurate record of the meeting.

We are also requesting that all persons making statements during the open public hearing disclose whether they have a financial interest in any medical device company.

Before making a presentation to the panel, please state your name, affiliation, and the nature of your financial interest, if any.

So far, we have listed for this session Mr. Angelo

Carrera from Beiersdorf-Jobst.

**AGENDA ITEM: Open Public Comment.**

MS. CARROLL: I am not Angelo. I am Madeline Carroll. I am a clinical therapy advisor of Jobst, the medical device firm headquartered in Charlotte, North Carolina.

My only financial interest is, I am a salaried employee. No stock bonuses.

I have handed the members of the panel my one-sheet recommendations. I have the five classifications that were sent to us by David Crouse.

You can see that in my recommendation, I have narrowed that five down to three, the reason is that, being a clinician, I would rather see the categorization of dressings done by the intended use of the dressing, rather than by what the dressing component is, or what the features are of the dressing.

In the simplified form I have given you, I have put the dressings that are mechanical barriers or primarily absorbers into one category, and then those dressings that are intended to be managed, or a micro-environment of the wound, or conducive to natural healing, as in most wound healings, to be in another category, with both of those being class I devices.

The reason I recommend the class I devices is that, for the extent of the use of these dressings, we don't really have any adverse events occurring, and the general controls should be sufficient to maintain the safety and efficacy of those devices.

The third group I have are those intended to be used as temporary skin replacements, especially those that are used over second and third degree burn injuries, such as the porcine one that we have used so many years in the past.

Our recommendation is for those to be class II devices, rather than class I, the reason being that -- especially in burn victims -- the use of temporary skin covering can, indeed, sustain a patient's life until other measures can be taken. That is our presentation.

DR. MORROW: Does anyone on the panel have any questions for Ms. Carroll at this time?

Is there anyone else in the audience who wishes to address the panel?

Seeing no one, we will now go to the open committee discussion and begin with the discussion of the classification of the five proposed categories of wound dressings.

We will start with the presentation from the Health Industry Manufacturer's Association. This will be followed by an FDA presentation and a reading of the FDA questions.

We will then have a general panel discussion of the topic followed by a specifically focused panel aimed at answering the FDA questions.

Before we complete the reclassification work sheets and the supplemental work sheet, we will have a second open public hearing. Then we will complete the reclassification and supplemental work sheets. They, and a vote, will constitute our recommendations to the FDA.

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

We will begin with the Health Industry Manufacturers Association presentation by Dr. Marlene Tandy.

**AGENDA ITEM: Classification of Wound Dressings.**

**HIMA Presentation.**

DR. TANDY: Good morning. I am Marlene Tandy from HIMA, the Health Industry Manufacturers Association.

On the agenda, you will see Mr. Stephen Peltier, as the speaker for this session. Unfortunately, Mr. Peltier had an emergency at his company yesterday and wasn't able to make it down. So, I am filling in for him.

I would also like to introduce with me, from the HIMA Wound Care Products Task Force, Anna McWright, director

of regulatory affairs with 3-M Health Care, who will be putting the overheads for us, and also at the table here, Jim Irvin, vice president of quality assurance and regulatory affairs at Smith and Nephew, Inc's Wound Management Division.

HIMA is a trade association representing medical device manufacturers. Since 1997, we have had a wound care products task force.

That wound care products task force consists of 18 companies -- and we are going to show you a list of companies in the next two overheads.

All of these companies are involved in wound care products generally. One of the focal points for the activities of the task force since it was formed, was to develop a classification proposal for the as-yet unclassified wound dressings, which is also why we are here today, to talk about that classification.

The HIMA classification proposal is something that you have in your panel packets, and hopefully you also have a copy of these overheads at your place.

The classification proposal that was put together by HIMA's wound care products task force -- and we did an initial submission and then, after we met with FDA and some health care organizations involved in wound care, we revised it. So, the revised presentation went in in January of this year.

It is comprehensive, in the sense that it addresses all of the as-yet unclassified wound dressings.

As Jim Dillard mentioned, there are really only five categories to be considered today, whereas there are a lot more wound dressings out there, as he referred to, some of the more complex wound dressings, that are not up for consideration today.

We included them in the HIMA classification proposal, but we will also be focusing on the five categories today, and obviously that is what is on the overhead.

I will say that HIMA's classification proposal looked at both the intended use of the products and also looked at the gap and severity of the wound, and looked at the risk posed by those products, in order to develop our classification recommendations.

That really is a basic concept of classification process, is trying to figure out what level of risk the product poses, and then match that to the appropriate level of regulatory controls, from the statute and the regulations.

We are in agreement with these five categories that are proposed today. I think they come from the past history, if you look at all the various classification proposals that were in the panel packet, where these types of dressings have been considered and proposed for classification, although not

yet finalized.

These categories do make some sense, although they do have significant overlaps. It is hard sometimes to carve out the universe of dressings, because there are so many, they are composed of so many materials.

What I believe from reading the past classification, that our task force spent a lot of time talking about is, how do you really slice up the universe into a rational group of dressings to be classified. So, we are going to look at these five today and give you our recommendations.

One of the hallmarks of a classification is that you have to have some type of identification of the category.

So, when you look in the federal regulations in the part 800 series and you see all the classifications of finally classified medical devices, they all have a description. I think they are actually referred to as an identification in the code.

They have a description of what the product is, what it does, and what class has been determined. So, we wanted to illustrate the definitions that have been proposed for each of these five particular categories.

These definitions come from the past proposals and from past panel considerations. I will not read these off, because you can go through these points here.

I will say, on this particular definition, that the important thing to note is the intended use of the product, the absorption of this type of product, and also the materials that it is made out of.

Those, on each of these definitions, are really the crucial parts of these product categories, what they are made of and what they are intended to be used for.

Next, we listed out some examples here. Some are relatively obvious, gauzes and sponges. We put island dressings in here. We wanted to try to be helpful and give some examples of the products that are out there on the market today that would fit in these particular categories.

The island dressing is something that usually is composed of some type of absorbent, simple material, kind of in the center, if you will, that is surrounded by an adhesive layer or backing or side piece.

In effect, it looks like an island, and it is a relatively large dressing. The terminology has grown up so that many clinicians refer to these as island dressings.

We believe that they would be an example of this type of product, in addition to those other types of products listed.

I think we can move now to the second type, the hydrophilic wound dressing. Again, it is sterile or non-

sterile, non-resorbable. These are features that many of these categories do share in common.

When we say no added drugs or biologics, this is to differentiate not just this category, but all of these categories today from what we have been calling these more complex dressings that are to be considered at a later date for final classification.

Those have generally been termed to be interactive, by virtue of the fact that they have some embedded or added material to the actual dressing, material to, if you will, interact with the wound itself. Those are the ones that you will be considering at a later date.

Again, the intended use for this category is to cover the wound and to absorb exudate.

We have some examples of these types of dressings. One example that may be a little bit unusual is the composite dressing, the one that is next to the bottom.

The composite dressing basically is a combination of these other forms of dressings, but the important point of a composite is that each component of the composite dressing does not really lose its own identity; it is a layered type of dressing.

Unlike some other types of dressings, where you might have one major material and the components kind of

interact with each other and form the dressing, these, the composite dressing, each type of dressing material essentially remains separate in layers, and can be a combination of any of these other types of dressings. Again, the thing that these things have in common is that they are hydrophilic, meaning that literally, they love water, for all you Latin people out there, who had to take Latin, like I had to in school.

Anyway, they draw water to them. That makes them, in effect, a very good absorption type of addressing.

The occlusive wound dressing, again, the important thing is the material that it is made out of, synthetics, polymeric materials. It may or may not have an adhesive backing. It does all of the intended uses that are listed there.

Again, in the occlusive wound dressing, we are getting into covering, and the occlusive nature of the dressing is not so occlusive that it blocks out the exchange of air in the wound, and allowing the exchange of air with the wound is an important factor in these types of dressings.

In particular, they are also important for dry types of wounds, where you might want to add some moist wound environment.

The examples here are listed. Now, you are going to

notice this, when I was first discussing this with our task force and learning about these dressings, that it seemed like there was a lot of overlap between a lot of the general examples here, like hydrocolloid, composite, hydropolymer, and the examples from the previous categories.

Again, there is a lot of overlap between the examples. Really, the reason for that is the type of categories that we are looking at.

These categories, the way they have been defined over time and the way the technology has changed, is that you may end up with more than one type of dressing that fits one or more of the categories.

Where they will end up, depending on which category they are in, is exactly what their intended use is, exactly what their labeling turns out to be, so less so the composition and more so the intended use.

That might make it a little bit cumbersome to deal with these categories, and past panels have had some discussion about trying to distinguish absolutely the categories from each other, so that nothing overlaps.

I think what we found, from reviewing the past panel transcripts and also the past proposals, is that it is very difficult, if not impossible, to get mutually exclusive categories in the wound dressing area.

Then we come up to the hydrogels, and the key thing about the hydrogel dressings, and why they have been carved out as a separate category, is the point that they are hydrophilic polymers combined with at least 50 percent water.

They essentially are like a watery gel. They are kind of a like a fluid, thick water-based type of dressing.

They in particular are good at providing water into -- well, to create a moist wound environment, so particularly to protect against desiccation and also to provide protection from fluid loss.

I think we can look at some examples. One thing I would like to point out in particular, that last bullet, the parenthesis about without active ingredients, again, that is to differentiate this group that would be suitable for this hydrogel wound dressing from the ones that are more complicated, that may be hydrogels, but that they would also have some additional active ingredient, an interactive dressing, if you will, that would provide more interaction with the wound itself and, therefore, be considered separately from what we are considering today.

Finally, the last category for today, the porcine wound dressing, is intended as a temporary burn dressing and made from pig skin.

I think there has been a little differentiation in

the past between temporary burn covering and a more permanent burn covering.

In the past classifications, the porcine wound dressing could have been considered with other materials for a more permanent burn dressing, and has been carved out as a separate category.

So, if you will, you can think of this category, although it doesn't say it in the official definition, it has been proposed as a more short term temporary type of dressing.

Now we are going to switch gears from the types of dressing and trying to look at what is similar about these categories, notice the overlap but also try to point out the differences. I am going to switch into our recommendations for the classifications.

We have already heard a bit about the classifications that are available, class I, class II and class III, from Jim Dillard's presentation.

We just wanted to summarize that class I products, which our recommendation today is going to be that all of these categories are suitable for class I classification.

Class I products all have some features in common. These are laid out here, and they are part of the law and regulation.

They are basically not life sustaining, life

supporting devices. They are low risk devices. In fact, they are the lowest risk category. Class I is the lowest risk category. You can't go below that in terms of risk.

The risk has to be considered based on what is the product going to be used for, what is the type of material.

In this case, we have been talking about wound dressing. What is the type of wound. We thought that was relevant and put that into our proposal for classifications, when you consider these areas of dressings.

These particular dressings, as you put it in the sheet before me, do have a long history of safe and effectiveness clinical experience.

Even though they haven't been finally classified into a regulatory classification yet, they certainly have been marketed products in all these various areas, and they have been used, as you have heard, with virtually no adverse reactions. Therefore, their long history of safe and effective use does make them suitable for a class I type of product.

A hallmark of class I is that those products are at such a low risk level that they can be regulated by general controls alone, and they are safe and effective at that level of regulatory control.

The next slide talks about what general controls

are. I think you have probably been through this in the panel training, so I am not going to go through each of these points.

The one I wanted to concentrate on is the 510(k) submission. Jim Dillard mentioned the new law, the 1997 Food and Drug Administration Modernization Act of 1997, which we refer to as FDAMA.

FDAMA turned class I devices into an exempt category of devices. What that basically said was, unless the device in class I is of such significance, a life sustaining or life supporting element, unless it has that level of activity, that class I is low risk enough that the devices in that class do not need to have some sort of premarketing submission to FDA, the so-called 510(k) submission.

Instead, they will meet all these other general controls, and that is sufficient to regulate these types of low risk products.

The rest of these are the regulatory requirements for general controls that you have heard about.

We think that class I, 510(k) exempt, is appropriate for these five particular categories of wound dressings, again, because one of the goals of FDAMA is to classify devices as at low a level of classification as their risk will allow.

A big part of that is because we don't need to be taking up all the extra resources for premarket review, premarket data, premarket submissions, for something that really is a low risk.

Instead, we can save the FDA resources, the review resources, the energy of the people producing these products for the higher risk class II and class III products.

To summarize, basically, these are the types of questions that the forms that you fill out to nominate a classification deal with.

We have basically talked about all of these, the fact that all of these devices are not life sustaining, or life supporting, they are low risk devices.

We do think that there is enough information, enough clinical experience, enough regulatory control at a general control level to put all of these into a final classification of class I.

This all means that we don't think they need special controls, that it would be some other post market type regulation, would be some other type performance standard.

Class II devices need some kind of special controls, but we don't think that is necessary here. We don't think that a performance standard is necessary. We don't think that a performance standard is necessary. We don't think that a

premarket approval application is necessary.

We don't think that there need to be any special types of restriction on the use or distribution of these products.

In summary, we support the classification proposal, that these five categories be considered today and classified as class I, 510(k) exempt products. I appreciate your time and would certainly be happy to answer any questions.

DR. MORROW: Thank you, Dr. Tandy. Does anyone on the panel have questions at this time?

DR. ANDERSON: In the classification, with the hydrogel wound dressings, the definition requires that these are non-resorbable matrix, the implication being that there is no biological activity.

How do we know, in this classification, that in fact, something is going to truly be better, that it might not have some subtle effect.

DR. TANDY: That is a good question. Since that is a very technical question, I am going to pass that on to either Anna or Jim to answer.

MS. MC WRIGHT: I think the nature of the material itself --

DR. MORROW: Could you please just state your name for the record and speak into the mike?

MS. MC WRIGHT: Anna McWright with 3-M. Your question, I believe, was about hydrogels. The general composition of hydrogels, as I understand it -- and I am not a chemist -- is that the components are really fairly straightforward chemicals, a lot of water in the matrix.

They have a long history of safety for each of these components and there has just never been any consideration that there would be an interaction with the body.

DR. MORROW: Any further questions?

Thank you. We will now continue with the FDA's presentation on this topic, which will be presented by Ms. Gail Gantt.

**AGENDA ITEM: Classification of Wound Dressings.**

**FDA Presentation.**

MS. GANTT: Good morning. I am Gail Gantt. I am a reviewer in the plastic and reconstructive surgery branch. I am also former exec sec of this panel.

Today we are going to discuss wound dressing classification for five of those wound dressing categories, and we are probably looking at one of the oldest medical products today.

This is showing the 16<sup>th</sup> Century Wound Man, which came from the ninth chapter of the History of Wound Treatment.

This wound man, probably back then, had therapies of

leaves, feathers, honey, tree bark, dried goat's dung, even boiled puppies, used on his wounds.

While this sounds like something like the witches' cauldron, it is all part of the wound dressing saga.

Today's wound dressing saga here begins 20 years ago when the general and plastic surgery devices were originally reviewed.

In 1976 and 1977, the general plastic surgery panel submitted a preliminary report on classification to the FDA in November of 1977.

The classifications were proposed in a January 1982 Federal Register notice. It is also in section G of the material of the materials you received from us.

Many wound dressing type products were also classified by the general medical devices panel. They were proposed in August of 1979, and finalized in October of 1980.

There is a copy of the Federal Register notice in section F of the material, and this is an overhead of those devices that were finalized in 1980.

I am just going to read through them briefly. they are liquid bandage, intravascular catheter securement device, medical adhesive tape and bandage, burn sheet, elastic bandage and skin pressure protector, and these are all class I. I will refer to the non-absorbable gauze later.

FDA withdrew the 1982 proposals except for non-absorbable gauze for internal use. The agency wanted the wound dressing categories as general as possible back then.

What followed was the general and plastic surgery panel met again in May of 1980, September of 1982 and May of 1985 to make new classification recommendations, but no finalized classifications resulted from any of these meetings.

In June of 1988, the Federal Register notice, which is in section 8 of the material, stated they would issue new proposals in a future FR notice.

However, non-absorbable gauze for internal use was finalized in a June of 1988 Federal Register notice, and it is listed there as well.

In September of 1989, we had a Federal Register notice published which issued new proposals and re-proposals for wound dressings. None of these were finalized.

Public comments were received on the 1989 Federal Register notice, and these comments centered on not requiring all dressing types to be sterilized, since preservative systems are used in some products.

Comments also centered on not restricting the size of products, to allow the use of synthetic materials in the composition of products, and to include non-living materials.

In 1994, many wound dressing products with 510(k)

exemptions were sent to FDA, and now those platform devices are exempt under 510(k).

What followed in July of 1995, the general and plastic surgery panel met to again examine wound dressing classification.

The comments at that meeting addressed issues of new material, materials versus use classification and the complexity of the wound dressing.

We also heard that the agency had an offering in 1980, 1988, final classification for some of the 1989 proposals for a number of years and it has worked well.

There was a concern expressed by the public that the agency was recommending dramatic changes.

We have also been working with HIMA in looking at classification.

Today we are going to look at five of those device categories. They are listed for you already, but I will just read them:

Non-resorbable gauze/sponge for external use; hydrophilic wound dressing; occlusive wound dressing; hydrogel wound dressing; and porcine wound dressing.

In reviewing risk, please consider the November 6, 1998 guidance for medical devices containing materials derived from animal sources.

This guidance document, which obviously has recently come out, addresses primarily bovine collagen and BFD. It also references other materials, which obviously include porcine wound dressings.

Pigs are known to contain several viruses which could potentially affect human cells: porcine parvovirus, porcine influenza virus and PER, porcine endogenous retrovirus.

We are currently unaware of data indicating that the viral indicators used in affecting sterilization standards will reflect the inactivation of viruses by either ETO or organosterilization.

This is of a concern, given these products are used in burn patients, who can be severely immunosuppressed.

This guidance addresses identifying all materials in a device from any animal source, by having a listing of tissue type, species of origin, country of origin and residence.

Other information we think should be considered should be the method of harvesting the tissue, monitoring of the herd, vaccinations, feed use, health of each animal and validation of device, manufacturing products, and either inactivation or removal of virus.

While going over the general device classification questionnaire and supplemental data sheets, we would like you

to keep the following questions in mind, and I will read those now.

Please discuss the proposed classifications for the five wound dressing categories. For the different wound dressing devices, what descriptive information and intended uses should be included in the proposed classification identification. This will refer you to question number four on the supplemental data sheet, and the five dressings are listed there.

Question number two. Please discuss the risks to health for each category of wound dressing devices. This will refer you to question number 5 on the supplemental data sheet, and the five dressings are there as well.

I guess now we turn the discussion over to the panel. Thank you.

DR. MORROW: Thank you. Does anyone have questions for Gail about this presentation.

DR. GALANDIUK: I have a question in terms of the composite dressings that you talked about. Where would that fit? Would that be a component of this?

MS. GANTT: Well, she mentioned things that we consider in the products, such as intended use. We also do consider materials within the composition of the product, the various types of wounds that you use supplies on.

You can classify a product into two categories if you choose. We tend to go with the predominant component, but we take all those three issues into consideration when we are classifying a product, or considering what is now a proposed classification.

DR. MORROW: Other questions?

DR. ANDERSON: If a product was classified into two different categories, then it would be the higher of the two that drives how the product is monitored?

MS. GANTT: The higher of the two, in actually determining the classification.

DR. MORROW: We are now going to start the panel deliberation portion of the meeting with a general discussion of this classification issue, rather than any specific responses to the FDA questions at this time.

**AGENDA ITEM: Panel Deliberations.**

DR. MORROW: Dr. Chang, do you want to open?

DR. CHANG: A lot of the information we had that was not really covered in the presentations were levels of risk. I think that should be a factor in determining the classification. If there is low risk, then this would tend to favor class I.

DR. MORROW: It was my impression from some of their summary material that they felt that the large clinical

experience had documented low risk. Is there anything else that someone would like to add regarding risk? Are there other panel members who are concerned about risk?

MS. GANTT: I just have a comment. What we did is we went back and looked at MDRs -- medical device reports. We went back five years, and looked at back to about 12 years worth of experience, just to see if there were any trends or any concerns, or what was happening in these five categories that we are proposing to you today. We did not find any significant issues.

DR. ANDERSON: Then, to clarify, from your review of the literature of their experience, all five of these categories would meet class I criteria?

MR. GANTT: I reviewed the MDRs in answer to your question. I just wanted to look and see what had been reported. The MDRs is probably a snap shot in terms of what may be associated with a product. It didn't give us the sense that there were serious issues that we needed to look at.

DR. GALANDIUK: Just one other question about the composites. I just have a concern that if you made a composite dressing using a hydrogel, or whatever, and a minor component, you could, if you had a new component, it is conceivable that you would have some kind of interaction that you didn't expect or wasn't previously known of, from this

mixture of new substances.

Would there be any control if these were classified as class I in terms of introducing new materials, to prevent problems?

MS. GANTT: Remember, we sent you the materials on the biocompatibility testing. Even if a product would fall into a class I exempt category, that doesn't preclude them from biocompatibility testing. They still have to test out the materials that they are going to use, for whatever their intended use for the product is.

That is, I guess you could call it a premarket screen to give us some confidence in terms of product safety.

DR. MORROW: Just to clarify, to make sure we have all got this down, the class I exemptions still include all the class I controls listed on all the slides that we received earlier today.

Is there other discussion from any of the panel members about this? Dr. Whalen?

DR. WHALEN: Just one brief question, maybe to Gail. The issue was raised about potential effects. Are you aware, is anyone in the room aware of any of the data which demonstrates potential adverse effects?

MS. GANTT: I am not aware of any data. Dr. Durfer, are you aware of anything?

DR. DURFER: I am not aware of anything at this time.

DR. MORROW: Other discussion? Dr. Boykin?

DR. BOYKIN: The only comment I have just concerns any intended use of the product. I think as we go along we can identify certain identifications that suit specific needs. I think it is important that we are relatively specific about that.

Other than that, I think there has been substantial clinical experience with all of these products to give us a level of confidence.

DR. MORROW: Any other comments? Ms. Brown Davis, do you have anything?

MS. BROWN DAVIS: No, not at this time. I don't know that we know of any potential difficulties.

DR. BURNS: I agree with all of the previous comments. My only concern is one that had been brought up, and that is new materials that might be proposed. I think that the general controls do ensure that those products would go through the same biocompatibility testing that other products would need, to ensure that they are safe.

DR. MORROW: Dr. Anderson and Dr. Galandiuk, do you have anything to add to your previous comments?

Okay. Having completed a relatively brief general

discussion here, we will now move on to focus our discussion on the specific FDA questions. If we could see those on the overhead, please?

**Agenda Item: Concluding Panel Deliberations:  
Completion of the Classification Questionnaire and  
Supplemental Data Sheet and Vote.**

DR. MORROW: As we talk about these questions, we need to consider each type of device specifically as we respond to the question.

So, if we start with the first question, please discuss the proposed classification for the different wound dressing devices. What descriptive information and intended uses should be included in the proposed classification identification.

At this point, we will ask each of the panel members to comment on these issues individually, and we will start just talking about item A, non-resorbable gauze/sponge for external use. Dr. Galandiuk?

DR. GALANDIUK: Which are we doing now?

DR. MORROW: We are not doing the question sheet yet. We are going through the FDA question which is related to that question sheet.

Could you just comment, for non-resorbable gauze/sponges, what descriptive information or intended uses

do you think need to be included with this classification.

DR. GALANDIUK: External use only. For internal use it would have the radiopaque markings for removal.

DR. MORROW: Dr. Anderson?

DR. ANDERSON: I have nothing to add to that.

DR. MORROW: Ms. Brown-Davis?

MS. BROWN-DAVIS: Nothing to add.

DR. BURNS: I think the classifications proposed by Gail Gantt are sufficient.

DR. WHALEN: Just one question. The internal sponge; are we discussing that?

DR. MORROW: No, we are discussing non-resorbable gauze/sponge for external use only.

DR. WHALEN: I have nothing to add.

DR. CHANG: Just one comment. The title specifies external use.

DR. MORROW: Maybe I could just ask for a little clarification here. Since we seem to be a little puzzle, perhaps it is because that particular item was rather self evident.

Could you just restate exactly what you want us to do here?

MR. DILLARD: There are actually two ways to approach this also. Perhaps I will give you an option so you

can deviate going through each one of these.

At your discretion, Dr. Morrow, you must also think about these as you are going through the sheets. What we can do is highlight the point where you get to question number four and question number five on the supplemental data sheet, to make sure you focus your attention on that, as you are going through each one of the particular product types, so that we don't have to repeat the effort, which you will repeat as we are going through the data sheets.

I will offer that up as an option. If you would like to do that, we can go straight to the data sheets and see what happens.

DR. MORROW: I think that the sense of the panel is that that would be particular worthwhile.

Okay, before we actually move on to filling out the sheet, it appears that we need to have the second open public hearing.

Is there anyone in the last half hour who has decided they would like to address the panel, or who was not here earlier and who would like to address the panel on this issue?

Okay, seeing no one, we will now proceed with the classification questionnaire and supplemental data sheet.

Ms. Shulman from the ODE, the reclassification and

classification coordinator, will help us if we need assistance as we go along.

After we have a discussion on the topics, we will fill in a panel consensus sheet, in addition to your individual sheets. Ms. Shulman will record this on the overhead.

At the end, when we have completed the questionnaire, we will take a vote and that will then become the panel's recommendation to the FDA. Is everyone clear on the process?

Okay, we are now going to go through the questionnaire. Now, we have before us the proposed classification of the devices and I gather you now go individually through each one of those items listed starting with external gauze/sponges.

So, the external gauze/sponges, non-resorbable gauze/sponge for external use.

Okay, question number one, is the device life sustaining or life supporting?

We will go around the panel beginning with Dr. Anderson. Will you give us a yes or no, please?

DR. ANDERSON: No.

DR. GALANDIUK: No.

DR. CHANG: No.

DR. BOYKIN: No.

DR. WHALEN: No.

DR. BURNS: I guess not.

MS. BROWN DAVIS: No.

DR. MORROW: Number two. Is the device for a use which is of substantial importance in preventing impairment of human health. We will start at the opposite end of that table. We will start with Ms. Brown Davis.

MS. BROWN DAVIS: What is the question?

DR. MORROW: Is the device for a use which is of a substantial importance in preventing impairment of human health?

MS. BROWN DAVIS: No.

DR. BURNS: I defer to the clinicians on that.

DR. WHALEN: No.

DR. BOYKIN: No.

DR. CHANG: No.

DR. GALANDIUK: No.

DR. ANDERSON: No.

DR. MORROW: Question number three. Does the device present a potential unreasonable risk for illness or injury. Dr. Anderson?

DR. ANDERSON: No.

DR. GALANDIUK: No.

DR. CHANG: No.

DR. BOYKIN: No.

DR. WHALEN: No.

DR. BURNS: No.

MS. BROWN DAVIS: No.

DR. MORROW: Number four, did you answer yes to any of the above three questions? No.

Is there sufficient information to determine the general controls are sufficient to provide reasonable assurance of safety and effectiveness.

Stated another way, if you answer this question yes, it will be classified as class I. Dr. Chang?

DR. CHANG: Yes.

DR. BOYKIN: Yes.

DR. WHALEN: Yes.

DR. BURNS: Yes.

MS. BROWN DAVIS: Yes.

DR. ANDERSON: Yes.

DR. GALANDIUK: Yes.

DR. MORROW: It appears to me, from looking at this form, that the remainder of the questions have become irrelevant to the discussion for this device.

We will now move on to the supplemental data sheet.

MS. SHULMAN: No, there is 11.

DR. MORROW: Can there otherwise be reasonable assurance of its safety and effectiveness without restrictions on its sale, distribution or use, because of any potentiality for harmful effect or the collateral measures necessary for the device's use?

Could you just clarify for us what this question is asking?

MS. SHULMAN: It is the prescription question. If you answer yes, then it is not a prescription device. If you answer no, then it is a description device and you go to 11b.

DR. MORROW: Thank you. Dr. Anderson, non-resorbable external gauze/sponges, prescription device?

DR. ANDERSON: Yes, we have adequate information.

DR. GALANDIUK: Yes.

DR. CHANG: Yes.

DR. BOYKIN: Yes.

DR. WHALEN: Yes, but for the record, I resent answering a question with the word potentiality in it.

DR. BURNS: I agree.

MS. BROWN DAVIS: Yes.

DR. MORROW: Okay, am I correct that we are now on the supplemental data sheet? So, we are still talking about external gauze/sponges.

We are the general and plastic surgery advisory

panel. Is this device an implant? that is the first question we need to answer.

DR. ANDERSON: No.

DR. WHALEN: No.

DR. GALANDIUK: No.

DR. MORROW: Okay. Indications for use prescribed, recommended or suggested in the device's labeling that were considered by the advisory.

Beyond the title of this device, non-resorbable gauze/sponge for external use, are there any other labeling considerations that the panel would like to address?

DR. GALANDIUK: I have one concern with the external use only. I have known of a lot of patients who get gauze/sponges that it heals into the basic wounds. So, I think -- I don't know if there could be some kind of guide as to deep external use versus a different use for packing, or is that not thought of as external use, packing.

DR. MORROW: Comments from other panel members on the packing issue. Dr. Whalen?

DR. WHALEN: I get the sense that for any degree of deep packing, that would not be considered. That seems arbitrary. I may be wrong.

DR. GALANDIUK: Still, external use is not a deep wound. Depending on how you consider it, that could be

considered external.

DR. GANTT: The reason why we put external use is because historically it has been associated with this category.

The internal use sponge has the radiopaque strip in it. That is the only reason why that is there. I think we kind of recognize gauze as a general use product and more specific attendant uses could be made. That is why it is there, because there is an internal use for it, but for packing, it would be used. That would be one of the ways it could be used.

DR. GALANDIUK: With more home health nurses and more home health services, it is becoming an increasing problem.

If there could be a statement, not to be used for deep packing--

DR. MORROW: Do you think that this is a provider specific issue or a device issue?

DR. ANDERSON: I think you raise a good point. For a really large wound where packing is involved, that could be a problem, if you left it in for a prolonged period in time.

I remember, in reading this over, that there were statements about what was temporary versus what was long term.

In the correct use of this material, we are changing

it at certain frequencies -- two times a day, three times a day -- which would get you out of this problem.

We wouldn't have a problem if we just said this is not for long-term use.

DR. MORROW: Other comments?

DR. BOYKIN: I agree. I don't think I would try to put a label on the time, but just basically call it a temporary external dressing. I guess that would be enough, a temporary external dressing.

DR. MORROW: So, the sense of the panel is that they would like to add to the title of this non-resorbable gauze/sponge for external use, a statement that this is a temporary --

DR. ANDERSON: Could we just say for temporary external use?

DR. WHALEN: I have a military background. In the military, what you see is gauze, cotton, and that is about it. The simplicity is there. I think it is intuitive, personally, the temporary use.

DR. GALANDIUK: I guess it is provider specific, but you see so much mis-use, could I suggest that this might be placed as a caveat in potential risks, that this could be put that these devices are not meant to be placed over wounds on the order -- many things could be incorporated in the wound,

so that could be more of a potential risk.

DR. CHANG: We try not to use it because of the potential risk of leaving it long term on a very deep wound, and if they are not there to oversee the changing of the dressing, they may not see that it is a deep wound. It is not purposely left on the wound.

DR. BURNS: Is this a problem with the current labeling or is this a problem more of inadequate training? It seems it is putting more of the burden on the labeling instead of the use being more of common sense.

DR. CHANG: It should be common sense.

DR. MORROW: Further discussion on this? Is the final sense of the panel that this is not something that needs to be included in a specific labeling recommendation, but we can list this under things that we discussed during our deliberations? Okay.

Are there any other comments regarding labeling that anyone would like to make before we move on to the next point? Okay.

Identification of any risks to health presented by the device. Dr. Whalen?

DR. WHALEN: No.

DR. MORROW: Other comments?

DR. CHANG: I would say at this point for foams

and/or cotton, gauze or sponges, there is the potential for incorporation of this device into granulated tissues. That may address the concern regarding this.

DR. MORROW: We are not doing foams right now.

DR. CHANG: Sponges, gauze or sponges.

DR. MORROW: Is there agreement with that?

DR. ANDERSON: I agree.

DR. GALANDIUK: Yes.

DR. MORROW: Are there any specific hazards to health that you would like to list for this device?

DR. ANDERSON: No.

DR. GALANDIUK: No.

DR. CHANG: No.

DR. BOYKIN: No.

DR. WHALEN: No.

DR. BURNS: No.

MS. BROWN DAVIS: No.

DR. MORROW: Now we come to the recommended advisory panel classification.

MS. SHULMAN: That is a high, medium or low priority.

DR. MORROW: So, we don't need a priority since this is class I.

Okay, item number seven is not applicable to this

discussion. So, we want to summarize our deliberations on which this classification is based. I believe we can say: extensive clinical use of these products in the absence of any significant evidence of risk would let us classify it as a class I.

Are there additions to that?

Identification of any needed restrictions on the use of this device. Do we have to do that?

DR. SHULMAN: If you refer back to 11-A of the general questionnaire, that is the description of it.

DR. MORROW: So, we have addressed this and said no. Okay, item number 10.

If the device is in class I, recommend whether the FDA should exempt it from registration or device listing.

DR. ANDERSON: All that means is that they have to register with you, the FDA, and say, we have this product and this is what it is. That is not a major burden.

DR. MORROW: Would you like to enlighten us, please?

MR. DILLARD: I really don't have much to add. Registration, listing, that the manufacturer is registered, that they are a legal manufacturer in the United States, or outside the United States intending to market in the United States, and that they are listing the devices that they are currently marketing. That is on an annual basis, that they

update that.

You are right, they would not have to come and register their manufacturing facility and list the product to FDA, because that is asking too much. Whether or not you think they need to do that in this case is what we are talking about.

DR. MORROW: We will start with you, Dr. Anderson.

DR. ANDERSON: I don't see any reason that they should be exempted from registering the product.

DR. GALANDIUK: I agree.

DR. CHANG: I agree.

DR. BOYKIN: I agree.

DR. WHALEN: I am supposed to give an answer and not a question, but the question is being raised if something can be exempted from this process.

It would seem to me if anything was ever going to be exempted from this process, it would be this. It seems so unburdensome that it would be registered. I guess I am asking the question, are there products that the FDA has exempted in the past?

MR. DILLARD: I am not going to answer that directly. I will answer the flip side, if you don't mind, which is almost all medical devices are registered and listed.

I don't know off the top of my head a clear example

I could give you of a product that does not require registration and listing.

DR. WHALEN: Let me ask a question. When we were talking about island dressings a while ago, that is something quite large. Are band aids listed?

MR. DILLARD: That is a good question. Yes, they are.

DR. WHALEN: Okay.

DR. BURNS: I agree.

MS. BROWN DAVIS: I agree.

DR. MORROW: Okay. The next item, should this product, non-resorbable external gauze, be exempted from premarket notification.

DR. CHANG: I have a clarification. Didn't the modernization act say that class I products would not need a premarket notification?

MR. DILLARD: The modernization act did designate that class I products would all be considered exempt.

What the modernization act gave us was an exception to make a case for why something should not be exempted if it is a class I product.

I think you have heard from some other discussions that it has to be some of the other criteria, about being life supporting or life sustaining, or be of substantial importance

to not allow impairment of human health, something that is a large public health concern, are really those products that could be considered an exception to that piece of the FDA modernization.

I think if your recommendation would be that the FDA needs to look at a premarket notification, I think we would certainly appreciate your input on what makes this of substantial importance, or why you think it meets a threshold of life supporting or life sustaining, so as to require a premarket notification prior to marketing.

DR. CHANG: So, in answer to question 10, yes. The non-resorbable gauze/sponge for external use should be exempt from premarket notification.

DR. MORROW: Could you provide the justification for that?

DR. CHANG: That the general requirements in class I would allow for safety and efficacy. A manufacturer, on its own recognizance, based on the registration requirements, can maintain quality.

DR. MORROW: Is there anyone who has disagreement with the opinion proposed by Dr. Chang, to exempt this from premarket notification? Okay.

Records and reports. Should this device be exempt from records and reports? Under this category do we mean

reporting of adverse events?

MR. DILLARD: Yes, record keeping in terms of manufacturing and adverse event record keeping and then reporting it to the FDA, yes.

DR. MORROW: Comments on whether this product should be exempt from this category? Dr. Anderson?

DR. ANDERSON: From my understanding, this would be like the first one. Of course, they should keep records of adverse events, as with any product, and I would have trouble imagining a product that you don't keep track of potential problems that come up with it.

DR. MORROW: Other comments on this issue?

DR. GALANDIUK: Couldn't those things be included in good manufacturing practices, like sterilized, and things like that.

MR. DILLARD: There certainly is some quality system regulation. I can't go into that in a lot of detail because it is not really my area.

I can say in general that part of the quality system regulations is looking at the various processes a manufacturer has in place to keep records, and that they have a process to analyze those records, and then decide whether or not it meets various other requirements for perhaps MDR -- medical device reportability -- to FDA.

That would be part of quality system regulation, too, that we would look at if we were to do a routine inspection or a targeted inspection.

This is specifically targeting that piece of it to say, do you believe the manufacturer doesn't need to keep records and doesn't need to go through that process, to look at reporting to FDA, as to whether or not it is a serious adverse event.

DR. GALANDIUK: What products don't need reporting, or are there products that don't report at all?

MR. DILLARD: That would probably be the same answer I gave before.

DR. ANDERSON: To make this quick, on the fourth point, good manufacturing practice, I would imagine -- who is exempt from good manufacturing practices.

MR. DILLARD: The other thing, of course, is that we now call it the quality system regulations. I am not sure that everybody understands that these forms are mandated from the Office of Management and Budget for us, so they change very rapidly.

We are referring to the same thing here, good manufacturing practice and quality system regulation.

The only difference here -- and it is a little bit of a nuance that might deserve a little bit of discussion is,

we mentioned training.

A class I device would not be subject to design controls, which is a portion of the quality system regulation.

I think at this point that there could be a product -- although, again, I am not aware of one -- where a panel may look at it and say, it is such low risk, we don't even think you need to be concerned with good manufacturing practices. Anybody can make this; it is not a problem.

Predominantly, that is what I would say that point is looking toward.

There is a product, 64-50 -- here is one example, a skin pressure protector. A skin pressure protector is a device intended for medical purposes. It is used to reduce pressure on the skin over a bony prominence to reduce the likelihood of the patient developing decubitus ulcers.

It is exempt from premarket notification requirements as well as good manufacturing practices, with the exception of one part of the good manufacturing practices regulations, part E-20.180, which deals with general requirements concerning record keeping and with respect to compliant class. I don't know if that helps as an example, but that is one.

DR. MORROW: So, to go back to the question on the table -- actually, we are still doing records and reports. I

think there was agreement that records and reports should not be exempted; is that correct? Was there any disagreement with that?

We are now onto what is listed as good manufacturing practice but which is now called quality standards. An example was just given of a device which was exempted from quality standards.

The question is, should these external gauze/sponges, is it the feeling of the panel that they should or should not be exempt from quality standards?

DR. ANDERSON: No, they should not be exempt.

DR. GALANDIUK: I agree.

DR. CHANG: I agree.

DR. BOYKIN: I agree.

DR. WHALEN: Agree.

DR. BURNS: Agree.

MS. BROWN DAVIS: Agree.

DR. MORROW: Okay, item 11. The existing standards applicable to the device, device sub-assemblies, components or device materials, parts and accessories. Is there anything anyone feels needs to be added under this heading?

Okay, am I correct in assuming that we have completed the forms for this?

It is my understanding from the executive secretary

that we will vote on these one by one, so that we do not become confused about what we are voting on.

Could we just see the overhead of what we said earlier in the discussion, to make sure that we are all voting on the same thing, please?

MS. SHULMAN: I just want to tell you, if you want to wait until you have discussed all five of them, you can vote on all five at the end.

DR. MORROW: Would that make everyone happy, to vote on all five of them at once? We will be taking individual votes. We will vote on all five at the end; thank you.

Everyone must fill out their own form and put their name at the top.

DR. ANDERSON: There is no spot for the name on the supplemental data sheet. Do you want us to put our names on that?

DR. MORROW: Please. Has everyone completed their paperwork? Good. We will now move on to the same process for hydrophilic wound dressings.

Actually, we will do hydrophilic wound dressings and take a quick break.

Hydrophilic wound dressing. Question number one. Is the device life sustaining or life supporting?

DR. ANDERSON: No. Can we do these in batches?

DR. MORROW: No. Is there any disagreement that this is not a life supporting or life sustaining device?

Is the device for a use which is of substantial importance for preventing impairment of human health.

DR. WHALEN: No.

DR. MORROW: Dr. Whalen says no. Any disagreement with that?

DR. GALANDIUK: I have a question. In the definition of impairment of health, does this have to do with the wound getting bigger and deeper? What does that impairment of health mean?

MR. DILLARD: This does require, I think, some clinical judgement. I will put it a little bit back on the clinicians here, I think.

Some of the keys, obviously, are substantial importance. I think it is one of those judgement calls. If you look at the spectrum of products that is associated with your practice, is this one of those things that you sort of think of as being directly attributable to preventing impairment of human health, or is it one of those things that you could think in your wildest imagination of some product failure, that it might then have some either direct or indirect impact.

I don't think that question is targeted at the

latter. It is more the former. It is certainly more of the more directly associated impairment.

MS. SHULMAN: I just want to add one thing. Questions one, two and three do pertain to the degree of risk of the device, and can be answered broadly.

DR. MORROW: We have a suggested response to question two, that the answer to that is no. Are you in agreement with that? Is anyone in disagreement with that? We are talking about hydrophilic wound dressings.

Okay, does the device present a potential unreasonable risk of illness or injury.

DR. CHANG: No.

DR. BOYKIN: No.

DR. WHALEN: No.

DR. ANDERSON: No.

DR. MORROW: Okay, we are now again on item 5. Is there sufficient information to determine that general controls are sufficient to provide reasonable assurance of safety and effectiveness; i.e., class I.

DR. GALANDIUK: Yes.

DR. ANDERSON: Yes.

DR. WHALEN: Yes.

DR. BOYKIN: Yes.

DR. CHANG: Yes.

DR. MORROW: I believe we are now on question number 11a, which is the prescription question. Without prescription, can there otherwise be reasonable assurance of its safety and effectiveness without restriction of its sale, distribution or use, because of the potential for harmful effect or the collateral measures necessary for the device's use.

DR. GALANDIUK: Yes.

DR. ANDERSON: Yes.

DR. WHALEN: Yes.

DR. BOYKIN: Yes.

DR. CHANG: Yes.

DR. MORROW: Other comments? Okay, we will now move on to the supplemental data sheet. Is this device an implant?

DR. ANDERSON: No.

DR. BOYKIN: No.

DR. MORROW: Okay, indications, recommendations or suggestions for labeling that should be considered for the use of hydrophilic wound dressings.

DR. BOYKIN: For external use only.

DR. MORROW: For external use only? Other comments regarding labeling?

Has there been identification of any risks to health presented by the device? Gail, is it safe to say that what

you told us earlier applies to all of the devices that we are considering in these categories?

MS. GANTT: Yes.

DR. MORROW: Hearing nothing, shall I take that as, we have not identified any risks to health presented by this device, and therefore, no specific hazards, the recommended classification is, thus, class I.

All right, we are now, I believe, again up to the summary of information that has led us to make this decision.

I think it is safe to say that the answer to this is similar to the previous one, that the extent of clinical experience and lack of adverse effects have led us to classify this as class I.

Are there any additions, deletions or other comments?

Identification of any needed restrictions on the use of this device. No.

We now need to discuss, once again, exemptions. The first of these is registration. Should this device be exempted from registration?

DR. ANDERSON: No.

DR. GALANDIUK: No.

DR. CHANG: No.

DR. BOYKIN: No.

DR. WHALEN: No.

DR. MORROW: The next is premarket notification.  
Should this device be exempted from premarket notification?

DR. ANDERSON: Yes.

DR. MORROW: Any dissent regarding that?  
Should this device be exempted from records and  
reports?

DR. ANDERSON: No.

DR. MORROW: Should this device be exempted from  
quality manufacturing standards?

DR. ANDERSON: No.

DR. MORROW: Are there existing standards which are  
applicable to the device, its sub-assembly or materials that  
the panel wishes to consider? No.

I believe that that concludes our discussion of  
hydrophilic wound dressings.

We will have a brief 10-minute break and resume here  
with occlusive wound dressings.

[Brief recess.]

DR. MORROW: We are now ready to do occlusive wound  
dressings, the third classification on your list. We will  
begin with the first question, is this device life sustaining  
or life supporting.

DR. ANDERSON: No.

DR. BOYKIN: No.

DR. MORROW: We have a no. Are there any comments, discussion or disagreement?

Is this device for a use which is of substantial importance in preventing impairment to human health?

DR. GALANDIUK: No.

DR. ANDERSON: No.

DR. MORROW: Okay. Does the device present a potential unreasonable risk of illness or injury?

DR. ANDERSON: No.

DR. MORROW: No. Is there sufficient information -- we are on question number five -- to determine that general controls are sufficient to provide reasonable assurance of safety and effectiveness?

DR. ANDERSON: Yes.

DR. GALANDIUK: Yes.

DR. CHANG: Yes.

DR. BOYKIN: Yes.

DR. WHALEN: Yes.

DR. MORROW: We have now again established class I. We are now on item 11a, the prescription question.

Can there otherwise be reasonable assurance of its safety and effectiveness, without restrictions on sale, distribution or use, because of the potential for harmful

effects or the collateral measures necessary for the device's use.

DR. ANDERSON: Yes.

DR. MORROW: We have a yes.

On the supplemental data sheet, is this device an implant? No.

Specific labeling considerations for occlusive wound dressings. Anything anyone wants to have considered for the label?

Have any risks to health been identified for this device?

For the record, the classification here is class I.

DR. CHANG: Just one other addendum on interventions. The risk to health would be, this occlusive dressing should not be placed on a known infected wound, to avoid creation of an abscess.

DR. MORROW: Are you recommending that as a labeling comment or simply as a listed risk to health?

DR. CHANG: Listed potential risk, not to add to the label but known identifications in the restrictions and the use, item nine.

DR. GALANDIUK: We could modify that by just saying temporary, because you could put it on an infected surface if it is for a short-term thing.

DR. MORROW: Other discussions from the panel?

DR. BOYKIN: The only comment is that we -- at least we try not to put occlusive dressings on contaminated wounds at all.

I think it would be worthwhile at least to point out the risk for abscesses and infections.

DR. BURNS: I just have a question. What is standard practice in this case?

MS. SHULMAN: I just want to clarify, I believe if you want to put that in, that would go under number 5 and we could take it into consideration. Question number 9 goes back to the prescription.

DR. ANDERSON: To clarify, this is a dressing that I use daily, but it is for sterile surgical wounds. At least, that is how I would use it.

So, I close the incision and now I want a dressing on top of it to seal it, as opposed to an infected wound that needs ongoing wound care.

DR. CHANG: My problem with not putting the potential risk if hydrocryloid(?) might be considered an occlusive dressing. There are different brand names for hydrocryloid.

If that is put on a partial fitness(?) wound, or stage two pressure ulcer, that may contaminate it. If it is

not checked at two or three days, we may have conversion from partial to full fitness wounds, which is a significant morbidity if you are talking about a four-by-four-inch area.

So, my comment is that this should be a comment with regard to specific hazards to health, the potential for creation of full fitness -- from partial to full fitness wounds, using an occlusive dressing, if care is not taken that this is not an infected wound.

DR. MORROW: A contaminated wound or an infected wound? Your example was a contaminated wound.

DR. GALANDIUK: I think that might go back to what was said about standard practice. You wouldn't normally leave an occlusive dressing on something that was contaminated or infected for a long time.

DR. MORROW: Dr. Boykin, did you have a comment?

DR. BOYKIN: It is a standard. The problem, of course, we see this from time to time in the community, especially with folks who are using these dressings who may not be under direct physician supervision.

They are putting them on surfaces that they can tell might be contaminated. It seems like a good idea because it is very wet or whatever the rationale is.

I think we should point out that these are not designed for use on contaminated or infected wounds. That is

not the intent of the application. I think we could just say that they are not designed for that application.

DR. WHALEN: I would think that the standard of care would be such that we would not be using these on contaminated wounds.

I would further suggest -- maybe somebody else has seen to the contrary -- that it is difficult to keep these on an infected wound. They slip off. Those are the ones that are the most moist.

I don't see where specific labeling has to come there, even though I fully agree with my colleagues that they should not be used on an infected wound.

DR. BURNS: I just have one more question as a point of clarification. What is done with this information, in terms of identification of any risk. Is this something that goes out on the labeling?

MR. DILLARD: This particular section is beneficial to us because as we are going through the classification process, one of the things that we have to do when we propose a class for the product is, we have to identify the risks.

Then we have to say which controls -- i.e., general or special kinds of controls -- control for that risk.

So, it does help clarify not only for us but I think for the general public, that you all have discussed those

risks. It is one of the things that we would note in a proposed rule for classification.

Then we would probably cite one of the general controls that you all have been talking about as saying that would be sufficient to control for that risk.

In your mind, if there is one, you can certainly identified that, once you have identified risk. If you think there is one applicable one in particular under general controls that would then cover why you have that risk, you could say that.

DR. CHANG: And to answer the question what happens, if we put in an item in question number five, is that incorporated into the recommendations for labeling or is that just a caveat in terms of indications, contraindications? What happens to these comments?

MR. DILLARD: We would use it -- again, the strict interpretation would be just in the classification of the product.

I think that just for example, some of the general controls, like the general control against misbranding or adulteration of a product, and that under general controls a product has to be properly labeled, and properly labeled for its intended use.

If that is something that I think is important, your

just mentioning it and bringing it up and having it in panel transcripts, and our mentioning it in a proposed rule, I think in a lot of ways heightens the awareness.

It wouldn't surprise me at all if the manufacturers wouldn't take that and say, well, yes, that might be a very good recommendation; that would be something that I would want to add to my product labeling, for example.

We would have less, again, premarket control if the product is exempt from premarket notification, of looking at that labeling and actually having a say in that prior to a product being distributed.

I think that is just, I think, a part of the reality of this process. So, it would not necessarily be a requirement, but we would certainly take all of this under advisement from you and see which tools might be the best way to use your recommendations.

DR. ANDERSON: I think the point has been very well presented about the issue that infected wounds -- also, the distinction between infected and contaminated wounds, because contaminated is a much broader topic.

I propose that we put under number 5 that this is not intended for use with infected wounds, and leave contaminated out.

DR. MORROW: Is there discussion about that

recommendation?

DR. CHANG: I think that is acceptable.

DR. MORROW: Other comments? All right, so we will amend number five to not intended for use with infected wounds, and I guess for the purposes of this document, since that is not an identification of risk; it is due to the problem of potential of causing full fitness injury.

We have classified as class I. We are now on number 8, summary of information. Again, extensive use and absence of evidence of adverse effects.

We previously said that there did not need to be restrictions on the use of this device. So, we are now to item 10.

Should this be exempted from registration or device listing? No.

Should this be exempted from premarket notification, which obviously bears upon the issue of the labeling, as just pointed out.

DR. ANDERSON: No, I don't think it should be exempted.

DR. MORROW: Other discussion?

DR. GALANDIUK: I think it should be exempted.

DR. WHALEN: In my own experience, I know these are overwhelmingly used to anchor IVs in place. I would venture

that in our institution that 95 percent of the use of these dressings is to anchor IVs in place.

In the context of that, two to three standard deviations of what the use is, I would suggest that it can be exempted.

DR. MORROW: Other discussion on this subject? I guess having heard a difference of opinion, we are going to have to have an official poll for me to fill in this item, since we are mass voting at the end.

DR. ANDERSON: I agree with the comment that was made. I withdraw my answer. I would point out that there is a separate category called intervascular catheter securement device, and it was previously defined.

DR. WHALEN: We are talking about what the FDA says it would be used for.

DR. MORROW: Is there anyone else who objects to the exemption from premarket notification for occlusive wound dressings?

Okay, records and reports. I hear a yes? Is there any discussion about that? In other words, this should not be exempted from records and reporting. I guess the answer really is a little confusing.

DR. GALANDIUK: It should not be.

DR. MORROW: Good manufacturing practice or quality

controls.

DR. GALANDIUK: It should not be.

DR. MORROW: It should not be exempt. Okay, existing standards applicable to the device, its components, parts or accessories. Any comments that you wish to include there?

All right, that completes occlusive wound dressings. We will now move on to hydrogel wound dressings.

Is this device life sustaining or life supporting?

DR. GALANDIUK: No.

DR. ANDERSON: No.

DR. MORROW: No. Discussion?

Is the device for a use which is of substantial importance in preventing impairment of human health? No. Discussion?

Does the device present a potential unreasonable risk of illness or injury?

DR. GALANDIUK: No.

DR. MORROW: Is there sufficient information to determine that general controls are sufficient to provide reasonable assurance of safety and effectiveness, the class I question?

DR. GALANDIUK: Yes.

DR. WHALEN: Yes.

DR. MORROW: Yes. Discussion?

Okay, prescriptions. Can there otherwise be reasonable assurance of safety and effectiveness without restrictions on the sale of hydrogel wound dressings, because of the potential for harmful effects or collateral measures necessary for the device's use. Dr. Whalen?

DR. WHALEN: If I can ask a question at this juncture, what is the current practice with these?

DR. BOYKIN: He asked for the current status on restrictions on hydrogels. Years ago they were under that, generally speaking. Now they are available.

Of course, when we do prescribe them, there are certain things that we are trying to document for medical necessity.

I think generally there are enough safeguards for us not to have to provide prescriptive evidence of the need for the device.

DR. ANDERSON: Could I ask for clarification from the FDA representative. What is being described is a non-resorbable matrix, the implication being that it is not something that would be taken up by the body through a wound.

I was told that some of these products have preservatives and other factors that go into it. I haven't heard anyone clearly represent how this is defined.

I am wondering, how does the FDA handle this problem? Is there anything that we should be concerned about?

MS. GANTT: When we looked at the proposed categories from 1989 in the Federal Register notice, we looked at the word absorbable and resorbable and went to Webster's dictionary to look at the term as it should be defined, and found that absorption was the taking up, and resorbtion was assimilation into the wound.

So, that is why we changed a little bit of the wording, to make it more in line with the definition.

I think when you look at the product, at least I think your question is going in the direction of delineating drug delivery versus a non-drug delivery system.

So, we look at the components within a product to see if there is any chemical effects exerted on the body.

Also, we looked at how the manufacturer is intending the product to be used and what our known information is on any of the components. So, those are all considered in terms of product evaluation. Is that what you are looking for?

DR. ANDERSON: If I am understanding you correctly, it is the obligation of the manufacturer to show that, in fact, there is nothing taken up by the body, the preservatives are not taken up, that there is no chemical effect.

If that were not the case, then the manufacturer is

liable for having misclassified that?

MR. DILLARD: This does somewhat go to primary intended use. It does have an effect on delineated whether or not something is a combination product or whether or not something is truly a device.

The point that you are bringing up is that there are preservatives that are added to wound care products and other products that are intended to preserve some effect of the device.

It is not intended to be added, to have some sort of biological or biochemical sort of effect.

The fact of the matter is, however, that in a lot of these wound care products, even if it is not a preservative -- let's say there is a monomer associated with the polymeric material -- some of that monomer may leach out of the wound care product and it may be absorbed or taken up by the body and it may have some sort of a biological interaction.

That is not the primary intended use of the wound care product. It is a secondary effect based on the components that are part of the make up of the product.

We do know about those kinds of effects. Plasticizers have an effect, and other things that are added to polymeric kinds of components, as well as these preservatives.

They are in such low concentration that we don't anticipate they are going to have an active biological effect. Yes, something biological does happen to clear them for example.

So, I think the delineation you are trying to make, or at least what I think I am hearing, is that you are concerned about those products that may have a concentration level associated with them, where there really might be a biological effect associated with the wound dressing used in a certain way.

Really, the products that we are targeting here are those that have such low concentrations that they are not intended to have a biological or a biochemical effect. That is not a primary intent of this category of wound care products.

Again, though, we couldn't say definitively that every component there is going to stay out of the body, stay out of the wound. There may be some leachates that enter, and that is part of, I think, the polymeric materials and some of the other compounds that we are using.

DR. MORROW: Even with the reclassification of this to class I, these would still be addressed for new products as they came to be looked at, which I think was the primary concern.

MR. DILLARD: Absolutely.

DR. MORROW: Okay, so we are back at question number 11a, regarding the need for a prescription or restriction of the use of this device.

Is there reasonable assurance of the safety and effectiveness of the device without restriction?

DR. GALANDIUK: Yes.

DR. MORROW: I have a yes. Is there any disagreement with that? Okay.

Is this device an implant? We are now on the supplemental data sheet. No.

Labeling considerations. Is there anything anyone feels should be appended to the label for hydrogel wound dressings? Discussion? Okay, no.

Identification of health risks presented by hydrogel wound dressing. Anything to be included here?

Recommended classification is class I. The summary of information, that is again the available extensive data from clinical use and the absence of identification of adverse effects.

We are now on item 10, should this device be exempted from registration and listing.

DR. ANDERSON: No.

DR. MORROW: Should it be exempted from premarket

notification?

DR. CHANG: Yes.

DR. MORROW: Yes. Discussion?

Records and reporting? Quality control practices.

DR. ANDERSON: No.

DR. MORROW: Okay, we will now move on to the subject of porcine wound dressings. Is this device life sustaining or life supporting?

DR. GALANDIUK: The panel said earlier that it was.

DR. MORROW: Discussion about this point?

DR. CHANG: I think there are many alternatives to porcine wound dressing that could fill in if necessary. My vote would be no, because there are so many substitutes.

DR. MORROW: Other comments?

DR. BOYKIN: I am agreeing with Dr. Chang, but I think we need to understand what this question is about. Is it looking at a situation or is it looking at this device?

DR. MORROW: I believe the instruction is the general and over-arching purpose of this device. Is it intended as a specific life sustaining product. Do we have any comment from the FDA?

MR. DILLARD: Yes, that is a correct interpretation.

DR. MORROW: So, I think that means not precisely for patient X,Y,Z in this particular circumstance kind of

thing.

DR. BOYKIN: Then I would say no.

DR. MORROW: Other discussion? Is there someone who strongly feels?

DR. GALANDIUK: I don't treat burn patients frequently, but would porcine skin products only be used on patients who are very ill?

DR. BOYKIN: You can use that but, as Dr. Chang has pointed out, there are lots of other things that we could use, including hematograft.

Again, the extent to which you would use it in a situation, I would just come short of calling it life sustaining. I think we have a whole lot of other things that we could employ besides pig skin to keep them alive and prevent fluid loss.

DR. MORROW: Further discussion? Is there a sentiment for answering yes, that this device is life sustaining? Okay.

Is the device for a use which is of substantial importance in preventing impairment of human health. Dr. Whalen?

DR. WHALEN: I have a little bit more trouble answering no to this question than I do to the first one. I am not necessarily appeased by the argument that there are

alternatives.

All alternative therapies equally address the same gravity of a problem, and not on the fact that something can be substituted.

My personal opinion on this one is that, while I have no difficulty answering no to question number one, I am going to say yes to question number two.

DR. ANDERSON: I am looking at it a little differently. If the issue here is what percent of the body burn the patient has, if this is a 70 percent body burn, then this is maybe the difference between life and death. If it is a five percent body burn, then it is not.

You could make the same argument about a swine Gantts catheter. If the patient is critically ill, then the swine Gantts catheter might be a life saving device. I don't think that is the spirit of this.

DR. WHALEN: The reason that I answered what I did, maybe it is just where I trained and the experience that I have, I wouldn't see anybody using porcine skin on a five percent burn.

DR. MORROW: Other discussion on this subject? I do not have a strong sense of the panel's feeling here. I am going to have to poll you one by one. Dr. Anderson?

DR. ANDERSON: You had to start with me. I am going

to say no.

DR. MORROW: So, you are a no. Dr. Galandiuk?

DR. GALANDIUK: I don't have sufficient experience with burn patients on that. I would agree with what Dr. Whalen would vote for.

DR. MORROW: So, you are abstaining.

DR. GALANDIUK: Yes.

DR. MORROW: Okay, Dr. Chang?

DR. CHANG: No.

DR. BOYKIN: I would say yes.

DR. WHALEN: I think I get two yeses; at least one.

DR. MORROW: Comments from our non-voting members about this issue?

DR. BURNS: I can't really comment, since I don't have any personal experience in this area. I would have to defer to my colleagues.

DR. CHANG: Could I ask what the FDA, what is the impact of this?

MR. DILLARD: One of the immediate impacts, of course, is that you are going to be going down a path in the flow chart that you guys haven't tested yet today. That is the immediate impact.

Other than that, I think that really these are kind of the global questions that really help formulate which class

the product should be placed in.

That is really the intention here. There isn't a hidden motivation or anything else. They are part of the tools that we came up with to kind of lead panels and lead us in the direction of where we can consistently say something ought to be designated as class I, II or III.

This is a tough question; I mean, I won't disagree. I think for this issue, it gives you a broad enough interpretation because -- for lack of a better word -- fuzzy words that are in this question, to be able to draw one's interpretation based on experience.

So, it is some indication, perhaps. Maybe one of the other things to consider is that for some indications you might answer one way and for perhaps another set of indications, there may be another way to answer the question.

That may be something else, because I did hear a little bit of a dichotomy that maybe under some circumstances you might say no and under other circumstances you might say yes. You might try to delineate those, too.

It is one of those questions that you have to look at and you have to use some medical judgement.

DR. MORROW: Thank you.

DR. ANDERSON: Can I ask Dr. Whalen, your argument is very well taken. So, a patient with very extensive body

burns, that is the one you would be selecting this porcine for.

What they are getting at is, then, based on that, we would then have to go through to say, what do we need to monitor to figure out if this is a problem or not.

What are you concerned about happening in the patient by virtue of using this porcine?

DR. WHALEN: To take one example, Gail in her exposition talked about infectious risk that may or may not exist, although there is no data to convincingly demonstrate that that is a clinical reality right now.

However, we are talking about a population of patients who have an overwhelming septic type problem. You really need to try to endeavor to sort it out, that this isn't the nature of the problem.

I think that this particular device is going to overwhelmingly be used for very complicated patients, in whom there may be infectious and healing complications that have not yet been carried out, despite a significant amount of data.

DR. ANDERSON: Dr. Whalen has convinced me and I will switch to a yes.

DR. MORROW: Dr. Galandiuk, having heard this additional information, do you have any desire to participate

in this?

DR. GALANDIUK: I am changing my abstention to yes.

DR. MORROW: Okay, so we have the sense of this committee that this is a device of substantial importance in preventing the impairment of human health, which means basically that you are saying this is not a class I device. No?

MR. DILLARD: I don't think you can quit say that yet. Maybe I would just recommend you go through the process and see where you come out.

DR. MORROW: Does the device present a potential unreasonable risk of illness or injury? No.

Did you answer yes to any of the above questions? Yes.

Is there sufficient information to establish special controls to provide reasonable assurance of safety and effectiveness.

If you answer yes to this question, check the special controls needed to provide such reasonable assurance for class II.

So, first of all, the first part of this question, is there sufficient information to establish special controls.

So, let me start, Dr. Whalen, you led the charge that got us here.

DR. WHALEN: I am the trouble maker. I hope that it will not be found entirely incompatible when I say that there is not, in my mind, sufficient information to make these kinds of decisions.

I have difficulty with the way that question two is worded. Because of the context of the usage, that is why I made the significant point to try to vote yes on that.

Extending that, when you look at the individual elements that are before us here, I don't think we have enough information.

DR. ANDERSON: Wait a second. If you are concerned about the immunocompromised patient who is critically ill that you are using this on, you are concerned about some unforeseen effect, like the infectious complications.

That makes sense. Shouldn't we be asking the manufacturer to do some kind of tracking to find out, at least temporarily, some type of study, to show that is not an effective problem.

DR. WHALEN: I think a case could be made for that. The question, I guess, in my mind revolves around whether or not -- it shifts to where the responsibility should lie.

Should it necessarily be inherent in the manufacturer to come up with this as opposed to those explanations and to utilize the substance. That is where I am

coming from.

I see this as a relatively minor facet in the whole complex of burn care, which is the only usage I have ever known for this device. In that context, I don't necessarily find it the manufacturer's responsibility. That is an opinion.

DR. BOYKIN: I just want to support Dr. Whalen. I don't think answering yes to number two implies a level of concern that causes us to get into this discussion where we have.

I look at the porcine skin as being an important device for preventing impairment of human health.

It is designed for critical illness, but I don't think -- we talked about life sustaining, not life supporting.

This is a very special device that is used in a critical situation. At the same time, I think we have had enough clinical experience with it to know that there may be rare cases of problems related to the immunocompromised patients. I don't see the need for putting that in special conditions.

DR. ANDERSON: As you read this form, if you look at their form, if you check yes to any of those three things, you are automatically down to number seven.

DR. BOYKIN: That doesn't mean that we can't say yes.

DR. ANDERSON: You did start there, and a yes to any of these automatically makes this class II, according to this form.

DR. MORROW: Not only that, however, if you read further on the form, having gotten to this point, you have a choice of saying either there is enough information that you know what you are concerned about and if you check yes, it becomes class II. If you check no here, it becomes class III.

DR. BOYKIN: This is very unfortunate.

DR. MORROW: We haven't finalized anything yes, if this causes anyone to re-deliberate on this issue.

MR. DILLARD: One of the other things, and what I hear you talking about -- and I am certainly not trying to put words in anybody's mouse -- but you are not only restricted to, on question number seven, to just what you see.

There may be other things that you think of that would help control for the risks identified, the issues that you are talking about.

Some of the other things that aren't on there are labeling controls, which is something else to think about.

Then, is the type of thing that you are talking about something that could be mitigated by some additional information in the labeling, some additional training. There are other options associated with what you might think are

controls.

DR. MORROW: Let me just ask a question for a minute to those who deal with burns most regularly here, which I presume are Drs. Chang and Boykin.

Given the fact that this is not a new product, but rather, something that is being reclassified, in your mind, is there sufficient concern that there are untoward effects of this product that are undocumented or unknown to us at this time?

DR. CHANG: There are not. I would favor keeping this in class I.

DR. GALANDIUK: A question. Provided that this is in class I, are these guidelines that were distributed to us still exempted for this product?

MR. DILLARD: Those are guidances. I don't want to get into a huge discussion, the difference between guidances and guidelines, but those guidances are intended to provide information to manufacturers when they are making the product.

All guidances are not mandatory. They are voluntary. We do have, though, available to us development of our own guidance documents for specific products.

We use guidance documents as special controls for class II products on a very frequent basis. That is another recommendation you might have, if you do end up with a class

II kind of recommendation, that FDA develop a guidance that can control for whatever it is, some of the risks or effectiveness issues that you might be targeting to.

I understand your quandary, Dr. Chang. I mean, it is a quandary, I can see, when you are looking at this.

I sense, at least from your comment, that you think it ought to be class I, but you can't answer question number two as no, and where does that leave us. I think that is a good question and I probably can't answer that.

DR. CHANG: To help clarify, there are guidelines or general regulatory guidelines for processing and labeling any animal derived products.

DR. WITTEN: I think Gail passed out the guidance that was recently published about materials derived from animal sources. That could be one of the special controls, if you wanted to answer question 7 by coming up with something. That is something that you could refer to, that you could use as a special control.

DR. WHALEN: This is really a question to Mr. Dillard, and I am sorry if it is going to be a difficult one for you.

When Dr. Morrow said, after we, for the first time today answered number four as yes because of question number two, so we are not going to be class I, you hastened to say,

that is not necessarily true.

Yet, it is designed to kick -- if question number four is answered yes -- to automatically make it a II or III.

Is it the intent of the FDA, as you understand it, that that is the case?

MR. DILLARD: I think that it is the intent of the FDA to again classify a product in the lowest class for the controls necessary, irrespective of this particular chart.

This is intended to help you guide your thinking, or help guide our thinking for classification.

There are some other cases where the form didn't exactly match what a recommendation of a panel might be.

I think we have taken those under advisement and we have come up with the final classification than necessarily what the panel might have come up with during their deliberations by going through the check sheet.

That is the reason I answered it that way. This is a recommendation from you, and all of your considerations and all the issues that you are bringing up, that we would have to factor into classification.

I think this is not necessarily a point that you have to get hung up on. It is one of those things that I think you can work through the sheet.

If your sense is that, even though you answer a

question a certain way that leads you in a way that you don't want to be led, I think that is a point that you can work through on the sheets.

DR. MORROW: I think if we could go back to where we were -- because I think clearly people's problem with this has to do with the severity of burn wound injuries for which this product is used, rather than specific concerns about the lack of information available about the product or hazards of the product per se.

We are being led down a path that I don't sense a great wave of enthusiasm for here. So, I guess we could look at this one of two ways.

We could say, in light of this entire discussion that we have just had, or people who felt that this is a device which is of substantial importance in preventing the impairment of human health, which none of us would argue with, but within the FDA's context of that statement, do you still want to answer that question yes.

If you do, we will then work our way through this sheet to make it reflect how we feel about this device.

DR. ANDERSON: The alternative would be to leave it class II but make this a very general surveillance special control, like what is defined by the animal things. Is this something that we can just leave it to what was passed out

here? This was for bovine serum albumen, but this is for the consideration of the FDA to decide.

MR. DILLARD: Yes, so in recommendations you might point to that guidance, or other guidances that might be appropriate.

DR. WHALEN: Since I sort of spearheaded this trouble, even though we are slightly outside the Beltway and not inside it, I am going to change from a yes to a no in fairly rapid sequence, because of the pragmatism that is inherent in that vote.

DR. BURNS: Just a comment about this work group guidance document. If we are going to try to consider this relative to any recommendations that are made here, I think it would be nice to have a chance to digest this. I don't think anybody has effectively looked at this.

I know that there are some animal products that are on the market that are not necessarily class II. My gut feeling is that the general guidelines that are there are out there that manufacturers are following would allow manufacturers to make these products, make them to the required standards.

Maybe this is an important product, but we don't need to go beyond the general controls.

DR. MORROW: For the moment, we will table any

discussion regarding those animal product guidelines until we sort of get to where we are going.

Dr. Anderson and Dr. Galandiuk, do you have any further thoughts about the question posed in item two?

DR. ANDERSON: No.

DR. GALANDIUK: I have actually, I guess now, become totally confused on my record keeping. The two of you and Dr. Whalen initially said that this device was important for human health.

DR. WHALEN: I am going to change my vote to no. On question two, I am changing my yes to no.

DR. CHANG: I want to clarify that. I initially said no, and looking down that flow sheet, I didn't want to be confronted with putting porcine grafts into class II or III by virtue of only two choices to question seven. So, my initial vote stands are no.

DR. MORROW: Further discussion from this side of the table?

DR. BOYKIN: This side of the table goes to no, although, I think we should, in fact, have some additional requirements so that it would be a class I with some additional documentation.

DR. MORROW: Well, we are not finished with the form in any way, and we certainly have the opportunity to add our

comments and concerns as we go along.

If you could please change our response to item number two to no, change our response to item number four to no.

We will now do item number five. Is there sufficient information to determine that general controls are sufficient to provide reasonable assurance of safety and effectiveness?

DR. ANDERSON: Yes.

DR. WHALEN: Yes.

DR. MORROW: We have now done a class I classification. We will now move to item 11a. Can there be reasonable assurance of the safety and effectiveness of porcine wound dressing, without restrictions on its sale, distribution or use because of the potential for harmful effects.

The answer to that question is no, yes, it does need a prescription. Is there any disagreement with that?

DR. GALANDIUK: No.

DR. ANDERSON: No disagreement.

DR. MORROW: We will now do item 11b. Identify the needed restrictions, that porcine dressing can only be prescribed upon the written or oral authorization of a practitioner licensed by law to administer or use the device.

Is that a restriction that people would agree with? I see some yeses. Is there any discussion about that?

DR. ANDERSON: This is a multi-check thing. It is not based on any of the other ones?

DR. MORROW: These items do not appear to be mutually exclusive.

DR. WHALEN: It would seem to me that checking one excludes two, but not three.

DR. MORROW: True.

DR. WHALEN: If you are only allowing a licensed practitioner, then the specific training gets thrown out.

My question relates to certain facilities -- and I will defer to my plastic surgery colleagues.

DR. MORROW: Is there agreement that everyone on the panel agrees with the first one, that it should only be given on the written or oral authorization of a licensed practitioner. Is that a true statement?

DR. WHALEN: It may be that it is only one. The question that I was going to ask is if at certain facilities it might only be recognized for burn patients.

MS. SHULMAN: The three build on each other. The first one is the basic prescription statement. The second one is in addition to.

DR. WHALEN: Then the first one shouldn't say only

you now.

That particular guideline from the U.S. Agency for Health Care Policy and Research states:

Studies on the efficacy of hyperbaric oxygen in pressure ulcer healing have been limited to case series of applying topical hyperbaric oxygen to a ulcer site.

The lack of controlled clinical trials providing the in vitro evidence suggesting topical hyperbaric oxygen does not increase tissue oxygen beyond the superficial dermis.

Those statements precluded the writers of those guidelines for any recommendations for the treatment of pressure ulcers to be made with topical oxygen.

On this slide, I would like to draw my conclusions that I have made from a review of the information that has been submitted from the 515(i) that you also received.

First of all, much of the literature concerning device performance was available at the time the FDA finalized its classification in 1988.

Since 1988, not much new data has been published concerning the clinical performance of these devices. In fact, the majority of the articles seem to have been prior to 1988.

In addition, it is difficult to interpret the device's role in wound repair. This is because many times

upon. Only excludes two.

MS. SHULMAN: Actually, two could be a smaller subset of one, and then not only do you have to be licensed, but you have to have some additional training to use the device. Then three, use it only in certain facilities, for example, an MRI.

DR. BURNS: I just have a question. What is the current practice for this?

DR. WHALEN: (Answer off microphone.)

DR. ANDERSON: Are you saying has to have special training or experience? So, you have to be a surgeon; is that what you are saying?

DR. BOYKIN: You should be at least familiar with how to use it, and that needs to come from either having been trained as a resident, or having someone monitor your first few uses of it.

We have, unfortunately, seem some situations where people haven't been trained trying to apply it.

DR. MORROW: Let me just ask you a question. Do you think there is a device for which that statement, that you ought to know how to use it, doesn't apply, as opposed to setting up a requirement for some kind of special training, as opposed to the concept of education.

DR. ANDERSON: We are all subject to malpractice

laws and lawsuits. If you misuse something badly and it is not general care, that is covered by this. You don't need to have a special FDA rule about that. Isn't that right?

DR. MORROW: The purpose of this is not to regulate medical practice.

DR. GALANDIUK: There are a few areas of the country where there are no trauma centers and where there is no special trained person. Other than having a licensed physician prescribe it, I don't think there should be a restriction.

DR. WHALEN: I would just still have some difficulty with the way the second one is worded. If we go away from the specifics of using pig skin on burn and put it into devices, there might be multiple instances where you could have a high school grad and you could special train them.

It would not necessarily be a licensed practitioner who also has specific training and experience. It just says a person.

DR. MORROW: Can we start, does everyone agree that you need to be a licensed practitioner to prescribe this, item number one? Is there any disagreement about that?

DR. WHALEN: Agreed. I don't see that two builds upon one. I see that it subtracts from one.

DR. MORROW: Now that we have agreed upon one --

yes, Mr. Dillard?

MR. DILLARD: I will just try to clarify a little bit, to just build upon what Margie said.

The intent of these is that the first one is the general prescription type of labeling, used on the order of a licensed practitioner.

Number is intended, under those circumstances, where you have a product that is a special kind of product that the company needs to do some sort of very specialized training, because it is much different than other kinds of products, or anything that has been on the market, that in your medical judgement, you believe the company needs to provide some sort of very specialized training, and that it is those people who get the specialized training, and only those people, who can use it.

So, it is one level more of restriction. Then the third one is even on top of that, which is that not only do people need to be trained that way, but there are only certain facilities that are qualified to then utilize that product also.

It is intended to build on each other. I don't want you to get too hung up on the wording, but that is the intent and meaning of those three, in terms of a hierarchical structure.

DR. MORROW: Thank you. So, going on to this second level of restriction, above and beyond the licensed practitioner, is there a sense that some formalized extra training is needed here?

DR. ANDERSON: Definitely.

DR. WHALEN: Yes.

DR. MORROW: Restriction to certain facilities?

DR. ANDERSON: No.

DR. MORROW: No. Okay. We will now move on to the supplemental data sheet. Is this device an implant?

DR. ANDERSON: No.

DR. MORROW: Okay, device labeling issues. Are there any comments to be included in the device label? Dr. Boykin?

DR. BOYKIN: Just a question. These are above and beyond what currently exists for this product; is that correct?

DR. MORROW: That is my understanding of it, yes.

DR. BOYKIN: If that is the case, then I think the current labeling is sufficient.

DR. MORROW: Any other discussion?

DR. CHANG: I second that.

DR. MORROW: Identification of any risks to health presented by the device.

DR. WHALEN: This, then perhaps with my pragmatic turncoat vote, is where we should list infectious diseases.

DR. MORROW: Could you be a little bit more specific?

DR. WHALEN: Infectious risks transmitted by the product itself.

DR. MORROW: And the potential risk or a documented risk?

DR. WHALEN: The potential risk. We don't have any data that would suggest it.

DR. MORROW: Other discussion about this point?

DR. BURNS: What is typically done for different types of products that are animal derived, especially if it is from skin? I am not an expert in this area of infectious viruses, but my understanding is that it comes from neural tissue as opposed to the skin.

Is there a real risk in that case, or in this case, for some sort of infection?

MR. DILLARD: I am going to introduce somebody on Dr. Witten's and my staff, Dr. Chuck Durfer, who I think will be able to answer some of those questions.

DR. DURFER: You asked a good question. Generally, when you deal with a product, you want to make sure that there are some sterile needs, not only an absence of bacteria and

fungi, but also other infectious agents.

On something like this, if you have a material that has a potential to contain a virus, you want to make sure that your processing methods are sufficient to remove those viruses.

Now, if I could ask you to restate your question?

DR. BURNS: I guess I asked two questions in there. One was what is done with other animal derived products that are on the market with respect to this.

Secondly, is there a real risk for an animal derived product that is from the skin for this type of transfer, or is it only a hypothetical risk.

DR. DURFER: Let me answer the second question first in terms of risk. Previously you asked with regard to the issue of MDRs.

I personally did not go back and review the MDRs on that. I do want to caution you, though. Ms. Gantt listed three viruses that we know affect people.

I know in terms of my reading of the transplant literature to date, the issue of the porcine endogenous retrovirus was only identified two years ago.

There is a hot debate now, even though it doesn't seem to affect human cells, there is a huge debate going on over interest in transplantation of porcine organs and

possible infection in humans.

From where I stand right now, I don't think we know, and given the fact that porcine endogenous retrovirus was only identified two years ago, I am not sure. So, it is a hypothetical risk? Perhaps.

In terms of what is normally done, I think that the guidance document is before you that you have not had time to peruse. I am sorry for that, it did just come out in the last week or so.

Generally, the approach has been to request, with bovine materials, requested that people not source it from countries that is known to have BSE.

Because other animals will have infectious agents, there is a real concern to try to find out where the animals are from, what do the animals eat, how is their health monitored, what was the veterinary care, was it a post-mortem or pre-mortem facility.

Even if you have a tissue-specific pathogen, the method of slaughter can be so that it might spread to other parts of the body.

Generally, we are concerned about making sure that every tissue is free of virus. That comes both from control of where the animals come from, and how they are processed, how the materials are processed.

DR. GALANDIUK: In the good manufacturing practices, would that be implied if you were making an animal product?

DR. DURFER: I, too, as Mr. Dillard, am not an expert in this field. I would say that at this point in time there are standards that are out there by recognized standard organizations -- ASTM, AAMI -- that show you sterilization standards. Those are the approaches that people will take with their products.

The standards are applied for validating the treatment of bacteria and fungi. The concern comes with the issue of virus and whether the indicators that are used -- bacterial spores -- are reflective of a virus.

At this point in time, I am personally not aware of any accepted standards for doing that. Instead, what you find is that there are a number of guidance documents out there that all give guidance in this area.

DR. MORROW: Would it perhaps resolve the panel's issue on this to note under item number five that the hazard of viral infection posed by this product is uncertain at present?

DR. ANDERSON: Yes.

DR. GALANDIUK: Yes.

DR. MORROW: We are up to item number eight, the

summary of information upon which this classification recommendation is based. Again, I think we have our favorite summary of this being a product which has been extensively used and problems not identified.

Number 9, we already identified needed restrictions on the use of this product, namely, prescription by a licensed practitioner, on a previous document.

Item number 10, exemptions. Registration and device listing?

DR. ANDERSON: No.

DR. GALANDIUK: No.

DR. MORROW: Not exempt. Premarket notification.

DR. ANDERSON: I guess I am kind of throwing this out, but my initial response is, I don't think this one should be exempt because where it is coming from, the country of origin and all that, may be a factor in this.

I certainly don't think we have assurances that this is okay. This is a little different than cotton gauze.

DR. BURNS: I think one issue with that is whether the QSR captured that information or not. I don't know the answer to that.

If it does, then that answers the question. If not, then you are probably right.

DR. MORROW: Does anyone know the answer to that

question?

MR. DILLARD: I don't know that there is a definitive answer. Of course, you look at the quality system regulation. It is a regulation of process control, more than it is specifics about what one does.

If a manufacture, for example in this case, identified the various viruses as a potential risk associated with a device, so they built into their process a way in which to check whether or not they have inactivated -- at least up to their own specs what they think they are inactivating -- they are probably going to be within the scope of the meaning and the intention of the quality system regulations.

Then again, if you have somebody who does not believe that that is an issue, or that it is all a hypothetical issue, and that they have other ways of controlling that risk, that may also be acceptable.

So, there are different ways to skin this cat, that may not up to what people's expectations are. Again, it is a process control and not necessarily a specific control that targets an issue like, are you looking at the company from whence the product is coming.

DR. GALANDIUK: What additional information would again be in the premarket notification?

MR. DILLARD: That is a very good question.

Relative to this issue, I take it. In this kind of situation, it is the guidance -- not only the one that you have in front of you, but there have been some other working paradigms, I think, and some questions, to address the issues that are presented in this guidance and in other guidances.

We would use those issues and we would raise those issues to manufacturers, and that would give us an opportunity to see whether or not they are aware of those issues, certainly.

I think that is what we have used in terms of premarket approval in the past.

DR. MORROW: In light of that discussion, is there a sense of the panel as far as whether or not the porcine dressing should be exempt from premarket notification?

DR. GALANDIUK: I think it should not be.

DR. ANDERSON: I agree.

DR. WHALEN: Not exempt.

DR. MORROW: Not exempt. Further discussion?

DR. CHANG: Just in terms of market, this may or may not play a factor, but I doubt that there would be an overseas competitor to midwestern sources of porcine skin grafts.

Therefore, this recommendation I think duplicates general practices already in place for safety.

DR. GALANDIUK: But we don't know which viruses

there are.

DR. MORROW: Other discussion? Phyllis, do I sense that you are not in favor of --

DR. CHANG: I would be in favor of the exemption.

DR. MORROW: In that case, let me just make sure that there are no other people who wish to dissent from this. Dr. Boykin?

DR. BOYKIN: No.

DR. WHALEN: No.

DR. MORROW: Records and reports; exemption? No.

Good manufacturing practice?

DR. ANDERSON: No.

DR. GALANDIUK: No.

DR. CHANG: No.

DR. BOYKIN: No.

DR. WHALEN: No.

DR. MORROW: So, we do not recommend exemption.

Existing standards applicable to the devices, its components, parts and accessories. Any comments to be included here?

Okay, that concludes our classification sheets, I believe. We are now going to have a mass vote on these five items.

Is there a motion from the panel to accept the classification work sheets as filled out with the

recommendation of class I for non-resorbable gauze/sponges for external use, hydrophilic wound dressings, occlusive wound dressings, hydrogel wound dressings and porcine wound dressings.

DR. GALANDIUK: So move.

DR. MORROW: Is there a second?

DR. ANDERSON: Second.

DR. MORROW: It has been moved and seconded that the wound devices just listed be classified into class I.

I now need to poll the voting members of this panel individually. Please give your vote and state the reason for you vote. Dr. Whalen, we will start with you.

DR. WHALEN: I vote yes for all five because of the preceding discussion.

DR. BOYKIN: I vote yes for all five for the same reason, and my general clinical experience with those devices.

DR. CHANG: I vote yes because of the evidence and discussions at these hearings.

DR. GALANDIUK: Yes, based on previous clinical experience and the discussions.

DR. ANDERSON: Class I, all five, the same reasons.

DR. MORROW: Dr. Witten, it is the recommendation of the panel unanimously that the five categories of wound dressing devices be classified as class I. Are there any

questions that you have for us?

DR. WITTEN: No.

DR. MORROW: Good, we will now break for lunch.

MR. DEMIAN: We will reconvene about 2:00 o'clock.

[Whereupon, at 1:00 p.m., the meeting was recessed,  
to reconvene at 2:00 p.m., that same day.]

A F T E R N O O N    S E S I O N    (2:03 p.m.)

DR. MORROW: I would like to call this meeting back to order and remind the public, again, that while this portion of the meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

We will now proceed with the first open public hearing session of the afternoon. Would all persons addressing the panel please come forward, speak clearly into the microphone, so that we can record your remarks for the record.

In addition, we are requesting that all persons making statements during the open public hearing disclose whether they have any financial interest in any medical device company.

Before making your presentation, please state your name, affiliation, and the nature of your financial interests, if any.

**AGENDA ITEM: Open Public Comments.**

DR. MORROW: At this time we have Dr. Lee Greenbaum to read a statement by Dr. Paul Sheffield. Please, come forward and do it.

DR. GREENBAUM: I am Dr. Greenbaum. I am the executive director of the Undersea and Hyperbaric Medical

Society. I will be reading a statement that was prepared by Dr. Paul Sheffield.

A question has been raised about the contribution to wound healing of topical oxygen versus oxygen that is inhaled.

The implication is that topical oxygen will diffuse beyond the superficial dermis to enhance wound healing.

I have been asked to describe my experience with measuring tissue oxygenation for both topical oxygen and hyperbaric oxygen.

Hyperbaric oxygen treatment is defined by the Undersea and Hyperbaric Medical Society as treatment in which a patient breathes 100 percent oxygen while the pressure of the treatment chamber is increased to a point higher than sea level pressure.

Topical oxygen involve surrounding the injured part with a plastic bag filled with a slightly higher percentage of oxygen than the atmosphere provides, and at a slightly higher pressure.

Proponents of topical oxygen often inappropriately refer to their device as hyperbaric oxygen treatment.

When the U.S. Air force Hyperbaric Medicine Center was established in 1974, patients breathed hyperbaric oxygen in a chamber pressured at 2.4 atmospheres.

Additionally, some patients received simultaneous

topical oxygen by an appropriate applicator -- plastic bag for limb wounds, plaster molds for torso wounds.

Within two years and after about 200 patients, the topical applicator was abandoned because it was clinically evident that it added little or no value to the hyperbaric oxygen treatment.

In a tissue oxygenation study, I used invasive oxygen electrodes to confirm hypoxia in chronic, indolent human wounds and to show that oxygen is delivered to wounds during hyperbaric oxygen therapy.

Topical oxygen was evaluated in only one healthy subject. In that subject, an oxygen electrode was inserted about one to two millimeters beneath the skin surface in the forearm, and a Topox topical oxygen control module was placed over the limb.

A normal skin PO<sub>2</sub> value of about 35 millimeters of mercury was obtained as the patient breathed air, and it did not change when topical oxygen was administered.

Conversely, when the patient breathed pure oxygen, there was a 10-fold increase in the skin PO<sub>2</sub>, to about 350 millimeters of mercury.

While inspired oxygen reached the skin, topical oxygen did not diffuse through the skin. I did not repeat this experiment in an open wound.

I recently published a review on measuring tissue oxygenation and found no oxygen data to support the hypothesis that topical oxygen improved tissue oxygenation to enhance wound healing. Thank you.

DR. MORROW: Thank you. Is there anyone else who wishes to address the panel during this session for public comment? Could you please come to the microphone, state your name and affiliation and any financial interests.

MR. WESTWOOD: My name is Joe Westwood. I am with GWR Medical, in Chaddsville, Pennsylvania. We are a manufacturer of disposable topical hyperbaric oxygen devices.

If I can have a few minutes, I would like to tell you why we believe that our topical hyperbaric oxygen is being used and has been for quite a few years.

I appreciate this opportunity to address your panel on topical hyperbaric oxygen. The role of oxygen in wound healing is well documented.

Cell metabolism in normal healing is significantly retarded in wound tissue. Oxygen tensions fall below about 30 millimeters of mercury.

GWR Medical has successfully treated more than 100 chronic non-healing wounds in the past two years with no adverse events.

These were all wounds that clinicians had concluded

were non-healing after months and even years of conventional therapy.

It is our belief that topical hyperbaric oxygen is a valuable adjunctive therapy to be used with good wound care practices, for example, moist wound healing, proper nutrition, and other recognized standards of care.

Although we have no new controlled clinical studies to offer at this time, we are scheduled to begin a 100-patient homeostasis ulcer study with Andrews Air Force Base later this month.

Dr. Carolyn Fyffe of the Bremman(?) Wound Care Center in Houston has prepared the study protocol for that study.

Dr. Fyffe is also the president of the Undersea and Hyperbaric Medicine Society, UHMS.

Large systemic hyperbaric oxygen chamber advocates, as you have just heard, question our use of the term hyperbaric to describe a procedure that operates at only 1.03 atmospheres of 22 millimeters of mercury.

Although this pressure is much lower than the two to three atmospheres that are used in the large full body chambers, it is essential, as I will explain in a minute, we believe, that we do operate at greater than one atmosphere.

The terms, in terms of normal baric and hyperbaric,

there is nothing in between as far as the dictionary is concerned.

We do not contend that topical hyperbaric oxygen will increase blood oxygen levels or non-wound tissue oxygen levels the way the more systemic chambers do.

However, there is strong evidence that oxygen applied directly to an open moist wound at a pressure greater than one atmosphere will increase surface wound tissue cellular oxygen levels.

I will try to explain the theory behind this and how it follows. The internal body pressure is equalized to the external pressure, normally one atmosphere. That is the normal state of events.

If the pure oxygen, which is 21 percent oxygen, is applied directly to an open wound at 1.0 atmospheres, there would be no diffusion of oxygen through the thin, porous membrane that makes up the cell wall.

Even though the partial pressure oxygen is higher than the outside of the cell wall, there is no driving force or difference in the total pressure from the outside to the inside to provide a driving force to cause diffusion.

The rate of diffusion, the gas across the thin, porous membrane, is proportional to this pressure differential.

Since nitrogen will diffuse more rapidly than oxygen using air at elevated pressures, it would result in only a small amount of oxygen passing through the cell walls.

However, when a slight amount of pressure -- 22 millimeters of mercury -- is applied to a 100 percent oxygen system, oxygen will diffuse through the cell wall and into the cell mitochondria, where it is available to support metabolism. We believe that this is the first step to the healing process.

The next step occurs when the external oxygen source is removed from the wound and the cellular oxygen level falls.

We believe the biochemical cytokines are produced which trigger the process of angiogenesis, or the growth of new capillaries. The body is simply responding to the perceived hypoxia that occurs when this is done.

The sequential increase and decrease of cellular oxygen level leads to healing. Research studies are now underway to confirm this proposed mechanism by Dr. T.K. Hunt.

Anybody who is in the hyperbaric field recognizes that name as someone who is well respected in the hyperbaric medicine field.

In summary, we can show you many case studies that confirm that topical hyperbaric oxygen is an effective adjunctive therapy for non-healing chronic wounds.

Soon there will be new clinical controlled studies to support this. We at GWR have a significant advantage over your panel. We know the therapy works. We see it happening every day.

I would like to leave with you, if I can, a couple of copies of some recent photographs of a patient who was treated with hyperbaric oxygen with a topical hyperbaric and with some pretty dramatic results. Is that appropriate at this point?

DR. MORROW: Yes, you can leave them and we will pass them around.

[Copies distributed.]

This was an open heart surgery patient with an infected chest wound. You can see the size of the wound and you can see the results of the topical oxygen as it was used over a period of about four months. It was the only adjunctive therapy that was used. One case. Thank you.

DR. MORROW: Thank you. Are there any questions for this speaker?

Is there anyone else who wishes to address this part of the meeting?

MR. LASLEY: My name is Bob Lasley. I am a retired ex-CEO and principal shareholder of Stevenson Industries, who have been manufacturing portable oxygen chambers for more than

20 years.

These are chambers made of rigid plastic, where oxygen is introduced into the chamber and raised to a pressure of 50 or 55 millimeters of mercury. At that point it cycles. Every 15 seconds it goes from atmosphere to 50. It cycles or pulsates.

Technically, it is hyperbaric. It sometimes confuses everybody because of the full body hyperbaric chambers.

We know a couple of simple things. One is that it works. Most importantly, it works. Right alongside that, it doesn't always work. It won't always cure every wound.

It cures enough of them to be impressive, and there are plenty of studies, none of them clinical and none of them double blind.

The industry just isn't big enough to support that kind of investment. It isn't going to happen unless Medicare approves topical oxygen.

More important than that, it is a very simple device. It is so simple it lacks respect. Going to 50 millimeters of mercury is equivalent to the pressure in a child's birthday party balloon. It is not much pressure.

The pulsation is necessary, we find, because it increases the circulation at the wound site and, more simply,

it does work.

Most importantly and far most importantly, within the 20 years, we have never heard of a single instance of anyone with adverse effects from the topical oxygen application.

If it doesn't work, it doesn't work, but there are no adverse events. Thank you.

DR. MORROW: Thank you. Is there anyone else who wishes to participate in this portion of the public forum?

Seeing no one else, we will proceed to the open committee discussion. We will begin the discussion of the classification of topical oxygen for extremities with presentations by Dr. Madeline Heng of the Veterans Administration Medical Center, UCLA San Fernando program, and Dr. Roy Myers from the University of Maryland Shock Trauma Unit representing the Undersea and Hyperbaric Medical Society. This will be followed by the FDA presentation and a reading of the FDA questions.

We will then have a general panel discussion of this topic followed by a focused panel discussion to answer the FDA question.

Before we complete the reclassification work sheet, we will have a second open public hearing, then complete the work sheet and vote on the work sheet.

Again, let me remind you that this portion of the meeting is open for public observation, with participation only at the request of the panel. We will begin with Dr. Heng.

**AGENDA ITEM: Clinical Experience with Topical Oxygen.**

DR. HENG: Good morning, Madalene Heng, associate professor of medicine, UCLA School of Medicine, and chief, division of dermatology at the UCLA San Fernando program.

I thank the FDA for inviting me to come before you and give you my 25 years experience in this area.

It behooves us to heal ulcers for a number of reasons. There is a risk of sepsis, the longer the ulcer remains unhealed, beside the risk of amputations, surgical flaps developing, and pain and suffering and escalating costs.

In a recent study of ours, it can decrease death rates five to seven times greater in patients with healed ulcers versus unhealed ulcers.

Because of the interests of time, I will focus my remark on just signs of topical hyperbaric oxygen wound healing and ending with a recent randomized, controlled trial of this technique versus standard wound care.

There are two kind of ulcers, ulcers that heal and ulcers that do not heal. The ulcers that heal, you can do

anything. You can put anything on them. You can almost spit on them and they will heal.

They contain adequate supplies of oxygen, of blood vessels that bring adequate supplies of oxygen to the tissues.

Ulcers that do not heal are either microthrombotic in the face of the ulcers cutting off the blood flow to the ulcers so that tissues die and become gangrenous, or there is an overgrowth of thick strands of collagen squeezing out the remaining blood supply.

All in all, there is a common denominator resulting in decreased oxygen flow to the ulcers, ending up with decreased oxygen tension in the tissues.

In order for normal tissues to grow and proliferate, you need at least 40 millimeters of mercury oxygen tension in the tissues.

In ulcers that do not heal, you have under 30 millimeters or mercury. In necrotic and gangrenous ulcers, this tension falls to zero to 13 millimeters of mercury, and you have gangrenous necrotic stuff covering the wounds.

Since man is an aerobic organism requiring oxidative phosphorylation to survive, in the low oxygen state, glucose cannot be metabolized through NADH and FADH-2 form ATP, through the glycolitic cycles and the krebs cycles.

In these oxygen states, free radical quenchers

reduced to the spots like dismutase, the capillaries are all used up because these cannot be generated in the absence of ATP.

In deep and necrotic wounds, they expose the underlying tissues to the oxygen in the air. You get a phenomenon called reprofusion injury. Reprofusion injury results from the generation of free radicals when oxidative phosphorylation resumes after a period of cessation.

Just to review the biochemistry, oxygen free radical generation, the generation of free radicals -- superoxide dismutase, single oxygen, hydroperoxone radicals -- are a normal byproduct of oxidative phosphorylation.

In the presence of adequate supplies of oxygen, you have also adequate supplies of free radical quenchers, as I mentioned, superoxide dismutase, catalases and reduced glutathione.

After a period of cessation of blood flow and a period of cessation of oxidative phosphorylation, the superoxide dismutase, catalases, reduced glutathione, are all used up.

When you jump start oxidative phosphorylation by supplying oxygen to the tissues, the free radicals are generated within milliseconds.

It takes 18 hours to synthesize one molecule of

superoxide dismutase by the reticulum. During this period, this lag period between generation of free radicals and accumulation of adequate supplies of superoxide dismutase, that may require many weeks, many days to weeks, to have sufficient supplies of the free radicals.

During this period, you kill tissues. So, the first step toward wound healing is the generation. A growth of new blood vessels cannot take place because as soon as you apply oxygen to the tissues, the tissues die, and this is what happens.

What happens when you supply hyperbaric oxygen to the tissues? Hyperbaric oxygen acts as a pseudo superoxide dismutase, cross linking the free radicals to mono unsaturated lipids, forming combination complexes. During this period, it holds the tissues, the killing effect of the free radicals at bay while it regenerates new blood vessels to bring blood into the tissues.

This is an example of such a wound, a wound that cannot heal, or is what we call a recalcitrant wound.

When you degrade this wound, the dead tissue reforms day by day and the wound gets deeper and deeper. Pretty soon you are down to the bone and tendons -- see the bone exposed. You get no mitosis because there are no active blood vessels.

The gangrene continues to extend and you get this

yellow necrotic slough, which is a sign of reproducing injury, and you cannot grow new blood vessels in such wounds.

When you supply topical hyperbaric oxygen treatment, within two and a half weeks, you get the first new blood vessels developing from day two.

This is two and a half weeks of growth. You see new blood vessels covering the bone. Within six weeks, this stage four ulcer is between stage two and three.

What happens if you give too much oxygen? It is not appreciated that oxygen is a toxic substance. If you give too much oxygen, you get a phenomenon called oxygen toxicity. You get generation of free radicals.

What is not very well appreciated is the mechanism of oxygen toxicity.

The body contains its ATP from glucose and its substrates. One molecule of glucose is metabolized to carbon dioxide and water, and 28 molecules of ATP in between the multiple steps that generate energy.

The energy generated from these multiple steps during the glycolytic cycles and krebs cycles is thought as 10 molecules of NADH and four molecules of FADH-2, to be converted to ATP when NADH and FADH-2 goes through the electron transport system.

If it does not go through the electron transport

system, the energy stored in NADH and FADH-2 is not converted into ATP. That is what happens in oxygen toxicity.

If the oxygen tension is too high, the energy is so high that it allows the electrons from NADH and FADH-2 to be transferred directly to molecular oxygen, bypassing the electron transport system.

So, you have done all this metabolism and have no ATP to show for it. It is like starvation in the face of plenty.

The other advantage of going through the electron transport system, besides generating ATP, is the energy difference is so high that it needs to be released in three different steps, which is done in the cytochrome system, so that the cell is not damaged.

If the electrons from NADH and FADH-2 is transferred directly to molecular oxygen, bypassing the electron transport system, the excess energy is released all at once in one step.

It is like a mini-atom bomb in the cell and it kills the cell. We call that oxygen toxicity. Besides your activation of glutathione peroxidase, which oxidizes reduced glutathione -- and, as I pointed out reduced glutathione is a free radical quencher of hydrogen peroxide radicals.

So, you decrease your supplies of free radical quenchers, also damage to SH containing enzymes, succinyl

dehydrogenase, a major enzyme in the krebs cycle.

Transaminase is very important to the wound healing, glutamine decarboxylase, a very important enzyme in the brain.

If you have low levels of glutamine decarboxylase, the patient is more likely to undergo epileptic seizures, which is what happens in systemic hyperbolic oxygen.

At seven atmospheres, you require only five minutes of exposure to oxygen to get epileptic seizures; at three atmospheres, 35 minutes.

With systemic hyperbaric oxygen, you do not have the risk of epileptic seizures, the toxicity to the brain, lungs and the eyes.

It is not clear how hyperbolic oxygen chambers work, because although the patient breathes in oxygen at 1.4 atmospheres, by the time it channels through those hundreds of miles of capillaries, it is no longer at 1.4 atmospheres; otherwise it would burst through the capillaries. The capillary pressure is extremely low.

What we think is happening is that the base of the ulcers is exposed to normal oxygen, but superoxygenated blood.

You run the risk of reprofusion injury. If you take off the dressings, 1.4 atmospheres is definitely in the toxic range.

The plus for disposable topical hyperbaric oxygen

bags is that there is no cross contamination between patients.

This is an extremely important concept which we had not taken into account in our publication in 1984.

This depicts the skin, the submeconium and the epidermis, with one capillary -- this is the arterial end of the capillary, the capillary loop, post-capillary venials.

The pressure within the arterial end of the capillary loop is 90 millimeters of mercury, post-capillary 22 millimeters of mercury.

In an ulcer, there is no skin, no meconium, and this is exposed directly to the oxygen and to the air.

Everything more than 22 millimeters of mercury will shut this thing down as though we put a clamp on the blood vessel and there is no blood flow.

We haven't appreciated this when we published our data, when we used 1.03 atmospheres, which is around 22 to 25 millimeters of mercury.

Although we healed wounds, we found that we healed wounds with scar tissue. Over recent years, we have modified our technique and we are capable of treading a fine line between reprofusion injury on the one hand, and oxygen toxicity on the other hand, so much so that we are able to produce wound healing, not only at a very rapid rate, but to

heal wounds without scar tissue.

I will show you our clinical results, ending up with our controlled randomized study.

This patient is a spinal cord injury patient at the level of T7, with unhealed ulcers for nine years, with four failed flap surgeries.

The stage two to three ulcers, going from perianal, is over the trochanthal regions, a huge ulcer, well over 200 square centimeters in diameter, one inch deep in areas.

This is after four weeks of treatment, perianal area. After seven weeks of treatment. If you feel the wound, it is absolutely soft, no scar tissue.

A diabetic with chronic renal failure, with osteomyelitis. They took off the infected bone down to the metatarsal heads. In the old days, this wound would have been treated with a below-knee amputation.

Look at the yellow slough, reprofusion injury. This will continue to expand and finally you have to chase the gangrene up the leg.

We treated the patient with hyperbaric oxygen. This is 5-19-97. At 6-3-97, two weeks later, we grew a good bit of granulation tissue and we were able to heal this wound without scar formation.

Diabetic chronic renal failure, bad nutritional

status and MRSA.

The technique is par excellence for burns. There is currently no treatment for burns, at least no treatment that will heal burns without scarring.

The patient of mine is a hair dresser. He also loves to cook. So, he was frying something in the kitchen and his pot of oil caught fire.

He decides to dump the oil in the sink. Bad idea. Spilled boiling oil all over his hands, and his hand caught fire. Third degree burns.

Within four days, we were able to decrease the swelling, decrease the extension of potential gangrene. It was starting to get all black.

In one week, starting to heal. Three weeks, wounds healed with no scarring, no loss of function. The wounds were so deep that he lost his pigment. But if you pick up the skin, the skin was as soft and as flexible as the good hand.

To show you my controls, the patient treated with six weeks of IV antibiotics, no change. Lots of scarring. This is just two pictures that we took in between 4-17-96.

Fourteen months later, still under that treatment, \$90 rental a day, not much change at all, in fact, a little bit more undermined and a little more scar tissue.

Another one of my patients, lots of scarring. Every

time we tried taking him off the low adovsfed(?), he will break down in a week.

The advantage of healing wounds without scarring lies in our ability to selectively grow new blood vessels that act as a cushion, so that the patient has his own adovsfed(?).

The wounds never broke out again. Lots of blood vessels are marred by scar tissue controls, lots of scar tissue. Any blood vessels that are present are squeezed from side to side by the scarring.

Another patient, lots of blood vessels wide open, increased density of blood supply. No scar tissue.

Controls, lots of new collagen regeneration, bands of new collagen. We have found in our experience that if you grow scar tissue together with endothelial cells, the scar tissue always outstrips the growth of endothelial cells and, finally, the healing of the wound will stop and the wounds will break down again.

These are the results of a controlled, randomized study performed at the VA. Pressure sores in both diabetic and non-diabetic patients, treated by THLP and standard wound care. Standard wound care included antibiotic therapy, IV antibiotics, low adovsfeds.

We compared stage two with stage three, with stage three and stage three with stage four. I showed you every

single patient.

We measured the size of the ulcers at zero week and at four weeks. If the ulcers healed within one or two or three weeks, they were considered healed at four. That is why the peculiar shape of the dots, because we would only take two dots.

Ninety-four percent of the patients' stage two ulcers, no matter how large, would heal within four weeks, and all ulcers were healed within six weeks.

In stage two ulcers treated by standard wound care, some ulcers healed, but other ulcers, we had absolutely no control over them. No matter what we did, the ulcers enlarged, from stage two to stage three to stage four, during the four weeks of observations.

Stage three ulcers treated by THOT, again, every patient improved. Stage three ulcers treated by standard wound care, a lot of patients got worse.

Stage four ulcers treated by THOT, again, every patient improved. We healed 17 percent of the ulcers within four weeks. In stage three ulcers, 29 percent were healed within four weeks, all were healed within seven to ten weeks. Stage four ulcers, we healed all ulcers except ulcers that had underlying osteomyelitis, ulcers in which the patient died of pre-existing cancer. Although the wounds were healing, the

patient died of disseminated illness before we could heal the wounds, and one patient died of expiration pneumonia.

Stage four ulcers treated by standard wound care, none of the ulcers improved. Every ulcer worsened within four weeks. I thank you for your kind attention.

DR. MORROW: Thank you. Are there any questions from the panel?

DR. GALANDIUK: I have a question. It seems like this compared topical oxygen rather than no treatment, where standard treatment consisted of the bed or antibiotics, as you said, where indicated. Were there uses of other dressing types or alternate products or something else along with that?

DR. HENG: We used only two types of dressings. We used -- if the wounds were purulent, we would use wet to dry saline dressings, and in topical hyperbaric oxygen, we would use gels while the wounds were healing and the discharged lessened because the wounds were healing.

We could not use products that contained oil because of lipid peroxidation. We allowed the standard wound care to use anything they wanted -- calcium aloginate, just everything has been tried. We threw the kitchen sink at these patients, so that they would heal. They were very ill patients with gangrenous ulcers, diabetic and non-diabetic patients.

At the end of this study, when we totaled up the

mortality rate, we found an increased mortality of five to seven times higher in our non-healing ulcers than our healing ulcers.

Everything is on the books. They were fighting for their lives. We gave them every care that we could.

DR. GALANDIUK: To compare them more completely, you would have to use the same kind of dressings.

DR. HENG: In our randomized study, we have used the same kind of dressings. Since our randomized studies, we have used all kinds of things. We could not heal wounds with dressings because, as I pointed out earlier, the first stage in wound healing was to grow new blood vessels.

These wounds could not heal because of reprofusion injury, and no dressing could grow new blood vessels under these circumstances.

If the wounds had a good blood supply, then you could do anything you like. You could give them platelet derived growth factor and they would increase the rate of wound healing.

The last thing you want to do to these wounds that are ischemic, that are starving for oxygen, is to invite all the neighbors in that have extra mouths to feed.

DR. MORROW: Thank you. Are there any other questions?

DR. BOYKIN: Dr. Heng, just a couple of questions. You showed a lot of work with topical oxygen and there appears to be some benefit. Are you saying that the primary rule of topical oxygen is to somehow accelerate healing in a wound that suffers from ischemia and reprofusion?

DR. HENG: There are two kinds of wounds, one that will heal and the other worsens, remains unhealed for many years, or develops a necrotic slough over the wound.

That is how we clinically identify those. Especially when we biopsy those wounds, we saw microthromba in the base of every one of those wounds.

DR. BOYKIN: What is the efficacy of the topical oxygen? How does it reverse the ischemia?

DR. HENG: In reprofusion injuries, if you can release free radicals and you have free radicals released -- in me, free radicals are released as a normal byproduct of oxidative phosphorylation, but I am not killed because I have adequate supplies of free radical quenchers.

As soon as the free radicals are released, a normal byproduct of oxidative phosphorylation, they are quenched as soon as they are formed; no problem.

After a period of relative hypoxia or ischemia, the free radical quenchers are used up because there is no ATP to generate more free radical quenchers.

When you supply oxygen to the wounds, you jump start oxidative phosphorylation. Free radicals are regenerated. At this time you do not have free radical quenchers to quench them, because it takes 18 hours to make one molecule of superoxide dismutase, and many days or weeks to have adequate supplies of free radical quenchers.

During this time you cannot grow one blood vessel, because as soon as you jump start oxidative phosphorylation, it dies. It kills.

DR. BOYKIN: How does topical oxygen improve that situation? You have details of pathology, but how does it improve it?

DR. HENG: It locks up the free radicals by cross linking the free radicals to mono unsaturated lipids in the base of the wounds and forming termination complexes between the free radicals and mono unsaturated lipids, holding off the destructive effects of the free oxygen radicals while the new blood vessels are being formed.

My data is showing the formation of new blood vessels is proof that we have been able to hold the free radicals at bay while the wound is healed.

DR. BOYKIN: I recognize the details of the biochemistry. But what you are saying basically is that the oxygen that you supply topically somehow acts as a free

radical scanner.

DR. HENG: Yes.

DR. BOYKIN: Do you understand that most of the basic research in that area would disprove what you just said?

It would show that additional oxygen will give you other types of radical intermediates, which will still require scavenging by other systems.

DR. HENG: Not when your pressures are very high. If you go very high, the oxygen toxicity itself forms free radicals, and we have found -- I cannot disclose our range because it is a proprietary range -- but we have found that it takes very little oxygen to go into the toxic range. Oxygen is truly a toxic substance.

DR. BOYKIN: I agree with some of the comments in general, but I am really talking about just very specific chemistry, the chemistry that we understand goes on in the body.

You may have a mechanism available for enhancing protecting the tissues, but what I am really saying is that I am a little in the dark as to how exactly this works.

That is what we are here to discuss, how it works. I am not pressing for any proprietary information, but you have answered my question.

The only other comment I have is this. You did

comment about a burn patient that you treated, and you made note of the fact that you had no bad scarring.

DR. HENG: No scar tissue.

DR. BOYKIN: You should also be aware of the fact that in the burn literature, a wound like that, that heals within three weeks -- and many do heal within three weeks without the use of topical oxygen or HBO -- with that type of wound, there is an 80 percent chance that they will not have a bad scar. That work was done by Dr. Titus in Louisiana.

I would be careful to use some of these clinical examples of wound healing to support theories about scar formation, when we have other clinical studies, without any special oxygen therapy, that will show us that we will get the same kind of results.

What is important here, what we have, is for us to decide if there is something about topical oxygen that we can identify that will withstand scrutiny, and that can face the risk benefit ratios that have to be made for medical devices.

I will comment on this a little bit later, but I appreciate your comments. I won't get into the biochemistry, but I just wanted to make those points.

DR. HENG: I just want to point out one thing. We did not come to a conclusion that -- we are different from HBO, by the way.

It is a new technology and we call this new technology THOT, to distinguish between all other technologies.

We did not come to the conclusion that it did not scar from just the clinical data. Every time we had a biopsy, it was the lack of collagen deposition in the tissue that we came to a conclusion that our technique did not scar.

Every other technique including the technique that we published in 1984 on which most of the THBO theories are based on my original work, produced this new recent advance in topical hyperbaric oxygen therapy, by using this technique, that we were able to heal wounds without scarring.

DR. MORROW: Thank you. Maybe we can continue on and carry on with any further discussion during the discussion part of the panel.

Next, we will hear from Dr. Myers.

**AGENDA ITEM: Studies with Topical Oxygen.**

DR. MYERS: My name is Roy Myers. I am a trauma surgeon at the Shock Trauma Unit in Baltimore, Maryland, at the University of Maryland.

We have been involved with wound management for over 20 years. I have an interest in hyperbaric oxygen therapy, and that is where I have become involved.

I have no interest in topical oxygen in terms of

financial gain or loss, and what I would like to try to present is that a lot of confusion currently exists, and is being promulgated again today, that topical oxygen is actually hyperbaric oxygen.

The key definition of hyperbaric oxygen is the breathing of oxygen in a pressure controlled environment which allows ultimately a transfer of oxygen through the lungs into the capillaries, where this oxygen is dissolved under pressure into the plasma.

Hyperbaric oxygen relates to plasma carrying oxygen. The consequences of increasing a pressure and a gas through an interface is that the gas dissolves in the fluid.

When we drink a cold drink of any sort, like Coca Cola, you do not see any bubbles in that fluid until there is a hot day and you shake it up and it comes out under pressure and it dissolves all over your hand. Basically, we relate to plasma loaded oxygen, which is then able to be transferred through the capillaries to all portions of the body, we believe, and to wounds where there may be a hypoxic basis.

I think that is the critical part to differentiate, and that as one is talking about topical oxygen application, the use of oxygen on an open wound under minimal increasing pressure, does not allow for plasma loaded oxygen.

I think that that differentiation is critical to the

discussion.

I do believe that in relation to any wound management, it is critical to have a good surgical team and a good surgical approach, and a lot of the delays in healing that we have noted in the past are changing with new techniques and the use of surgery to excise, or a person to excise dead tissue, that has to be removed for wound healing to occur.

In any of the settings of the wound progression, I think it is important to have standardized the surgical approach as well as the wound dressing approaches.

What I would like to present is some work that we did a number of years ago, working in one of the rehab hospitals that I was involved with, and our management of chronic, non-healing wounds.

In this situation, in the sense that it was a rehab unit, we did have control of patient management, care, dressing, and also we were able to engage in appropriate pressure release on these wounds, so that we were trying to standardize a general approach to the wounds.

In this study, we looked at patients with these chronic wounds and treated patients with topical oxygen or topical air, so that the pressure surrounding the wound was either air, with 21 percent oxygen, or 100 percent oxygen.

We also looked at the transcutaneous oxygen levels in two groups of volunteers, again, through the human volunteers release research committee.

We looked at oxygen levels in the tissues using the chest as a standard reference and a limb as the other location.

We looked at the tissue levels when the person was breathing air, breathing oxygen, breathing air with a topox on their limb, with oxygen surrounding that limb, or with air surrounding that limb.

Then, finally, we took the second set of volunteers into a hyperbaric environment, doing the same.

What I would like to show now is what our results were. The top level, the underlying mark, the 79.5, represents our chest O<sub>2</sub> level, 68 is the foot level.

When we placed that person with no Topox, just free of anything, just measuring their lungs on air in the first slide, letting them breathe 100 percent oxygen via a head tent, which ensured 100 percent oxygen, the head tent is placed around the head. There is a soft rubber diaphragm collar that fits around the neck, and it assures no leakage of oxygen.

You can see that the tissue oxygen levels were raised dramatically to 479 on the chest and 263 on the leg.

It is always noted that the chest levels are significantly higher than the leg, because of underlying muscle profusion, skin profusion, and it is a very significant level. Our n in this particular case is 21 volunteers.

As we go further down the line, what we then did was said, what if we deliver oxygen in the Topox. You can see that when the Topox is functioning in the fourth column along, the O<sub>2</sub> level is 153.

Now, there is, then, a significant difference between the O<sub>2</sub> tension with air circulating or with oxygen circulating, as compared to the normal level in that tissue where oxygen alone is breathed. Something is happening in that limb with the application of Topox.

I believe what is happening is that as you cyclically inflate the balloon part of the Topox, you are causing a venous obstruction.

This venous obstruction is related back to a slow phase of flow through the limb, and you are actually recording a decrease in oxygen levels from your standard oxygen breathing without the Topox.

When you use air versus oxygen, you can see that the levels are even lower than the standard level of nothing.

Again, what I think you are doing is you are inhibiting oxygenation through the tissues through the

pneumatic effect of the Topox.

Looking at the O2 levels in air, circulating, the Topox bag, the O2 levels with O2 circulating in the bag, between the two, there is not much difference. However, it is significantly different to no topox.

Whether you use air or oxygen as your pressure modality with the Topox on, you still get a diminution in the amount of oxygen measured by a transcutaneous monitor of that leg.

We then took the next step of looking at these patients in a hyperbaric environment. We started off by standardizing, again, our tissue oxygen level in the leg, 67. This represents the mean of 11 patients.

On air, the level of oxygen is 58. On oxygen, circulating the Topox, it is 57. Again, the levels drop when you apply Topox.

When you look at oxygen breathed in a hyperbaric environment at two atmospheres of pressure, which is then the equivalent of 33 feet of sea water pressure, with 760 millimeters of mercury pressure, a significant difference from the pressure by the topox itself.

you can see that the tissue oxygen level dramatically increases from the 67 to the 260, as compared to the chest, which is higher anyhow.

When you now start looking at the levels in the topox compressed limb, you see that they have dropped from the 260 with no Topox on the right side there -- the last three columns -- and the levels with Topox on air, and Topox on oxygen.

In essence, again, in the hyperbaric environment, we are able to show that the Topox seems to inhibit the increase in oxygen.

However, the oxygen levels under hyperbaric conditions, with or without Topox, are significantly increased from the normal of 67.

Comparing Topox air, Topox oxygen, not much difference, but significantly different from the Topox on surface oxygen, surface air.

So, what I think we have shown is that there is a dramatic oxygen increase in the tissues using either the breathing of surface 100 percent oxygen, or 100 percent oxygen in the hyperbaric environment.

Now, then back to our trial. While we were in the rehab unit, we took the chronic non-healing wounds. The first group was treated with -- this is on a randomized fashion on random numbers. The patients were allocated into the two groups.

If a patient had two limb ulcers -- in other words,

left and right leg or arm ulcers -- they were treated one with oxygen, one with air, as the Topox compressor.

The wounds on the left side, the air group, there were a total of 24 patients. Looking at them in a healed or improved -- again, it was over a three week to six week period that we saw these changes -- 79 percent of the air patients healed their wounds or improved their wounds.

Using Topox with oxygen, 76 percent of the 17 patients healed their wounds. Those who failed -- and failure we defined as re-amputation or a higher amputation -- were 24 and 21 percent.

So, in essence, what we were able to show is that there was no improvement whether we used air in the Topox or oxygen in the Topox.

All other things were equal. The same surgeon was involved with debris-ing. The surgeon did not know whether the patient was getting air or oxygen, and the patients were randomized into the trial per random numbers.

My assumption then was that we were not getting sufficient oxygen into the wounds to heal it, as per our present understanding of tissue levels of oxygen and the importance of capillary eroded oxygen through the plasma.

How could we say the wounds healed if they healed any faster than non-treated wounds. Maybe the pneumatic

compression could be driving through part of the wound so that the transferred distance of oxygen from the capillary to the healing edge was reduced and, therefore, indirectly increased the tissue oxygen within that wound.

The only other thing we could have done we did not do was treat anyone with the Topox, and had a third group which would have been appropriate, equal surgery, and appropriate wound dressings.

Our dressing changes were actually wet to dry saline dressings, debris removal as needed, and none of them required skin grafting. Are there any questions?

DR. MORROW: Thank you. Any questions for Dr. Myers? We will take further discussion at a later point in time.

We will now hear from Dr. Durfer from the FDA.

**AGENDA ITEM: FDA Presentation.**

DR. DURFER: Good afternoon. Today I will be commenting on issues associated with a possible reclassification of topical oxygen chambers for extremities.

The definition of topical oxygen chambers for extremities is found in 21 CFR, part 868.5650, as displayed on this slide.

Of note is the hermetic sealing of a patient's leg to a supply of oxygen just above atmospheric pressure on

chronic ulcers. This device is currently class III.

The next slide shows you some regulatory history of these products. The product, in 1976, when the medical device amendments to the FDA&C act were enacted, topical oxygen chambers for extremities were already in distribution. Hence, they are pre-amendment devices.

In October of 1977, the general and plastic surgery devices panel met and recommended that these products be determined to be class III medical devices.

FDA concurred, and in 1982 the products were proposed, and a Federal Register notice was released that proposed topical oxygen chambers for extremities as class II medical devices, and I will discuss more about that in a minute.

Six years later, after reviewing the comments received about its proposed classification and a re-evaluation of the scientific literature -- in 1988 FDA finalized classification as a class III medical device. This will also be discussed more.

Finally, in August of 1995 and in June of 1997, FDA requested through Federal Register notices information about the adverse safety and effectiveness data on topical oxygen chambers for extremities.

It is also important to note that full body

hyperbaric oxygen chambers are viewed by the FDA as a different medical device, which are class II medical devices as defined in 21 CFR 868.5470. The definition of those products is on this slide.

The next two slides are to help you understand the ramifications of your decisions today.

If the device remains a class III medical product, FDA would make a call for PMA applications from each sponsor, which would provide sufficient scientifically valid information to document the safety and effectiveness of the device.

In addition, after a transition period, further commercial distribution of these devices would be prohibited until the FDA approved a PMA application for each device.

If these devices are reclassified to class II medical products, then new products will be commercially distributed after the review of a premarket notification application, or a 510(k) application.

This application would need to demonstrate the substantial equivalence of the new product to another legally marketed device.

Our next two slides show you some of the indication for use statements on recently cleared products. I will also show you that currently there are eight manufacturers for

which 510(k) applications have been cleared.

Here are some of the indications for use, and these are the most recently cleared products, as adjuvant therapy in wound management and treatment, and indications for use in surgical wounds, pressurized ulcers.

On the next slide is a review of the medical device reports received for this product area, from 1984 through 1998.

It is very likely that the first two medical device reports listed up there were actually mis-categorized. This is just a reflection of what we downloaded for topical oxygen for extremities.

The first two were probably mis-coded and may well belong in the category for full body oxygen chambers.

However, there are a few conclusions that could be drawn. Even though we don't know the full number of products that are in use at this time, that would form the denominator for a risk benefit assessments, it would appear that the number of adverse events is extremely small for this product category.

On the next slide, I would like to discuss a little bit more the issues associated with device classification.

On October 6, 1977, the general and plastic surgery devices panel met and recommended class III status for topical

oxygen chambers.

The panel based its recommendation on the members' personal knowledge of, and clinical experience with, the device and upon a review of the literature.

The literature articles that are cited in the 1982 Federal Register notice as a basis for this I have shown on this slide.

FDA concurred with this recommendation and proposed a class II status for this product, with the following safety concerns being measured.

Those risks were the risk for fire and explosion, infection transmission either from one patient to another, or from one patient to themselves, and injury was often from improper levels, which of course must be controlled.

Six years later the FDA finalized the device classification, and identified topical oxygen chambers as class III devices.

As stated in the Federal Register notice of 1988, the agency believed that they did not adequately take into account the lack of scientific evidence in support of the safety and effectiveness of the device.

This conclusion was based upon two major publications which are also referenced in that 1988 Federal Register notice. I will read you essentially what the notice

states.

First, there was a review of the literature by Dr. Max Cohen, who was a consultant to the National Center for Health Care Technology.

He: "found little valid scientific evidence to support the safety and effectiveness of use of the topical oxygen chamber for extremities" for the treatment of decubitus ulcers.

Dr. Cohen's review of the literature found no studies comparing the results of treating bed sores with topical oxygen chambers for extremities with the results of treating bed sores by exposing the ulcers to topical air.

Thus, Dr. Cohen concluded that valid scientific evidence had not been provided to establish the effectiveness of the device. That is from the 1988 Federal Register notice.

The second document cited in that notice was a 1988 unpublished draft assessment of the value of topical oxygen therapy in the treatment of decubitus ulcers and skin lesions conducted by the Office of Health Technology and Assessment of the Public Health Service.

The Federal Register notice of 1988 states that studies demonstrate that wounds that are often unresponsive to previous treatment heal following topical oxygen therapy.

However, a number of uncontrolled variables make it

difficult to attribute the healing to use of topical oxygen.

According to OHTA, use of topical oxygen in the treatment of pressure sores and other skin lesions does not appear to be a widely accepted practice among members of the medical community.

The following slide shows some further issues why the FDA felt that it should be a class III medical device.

The FDA believed the device had the potential for widespread use in the elderly and the infirm, even though there might be a lack of valid scientific evidence.

Therefore, the device presented a potential unreasonable risk of illness or injury to patients if there were not adequate data showing device safety and effectiveness.

Therefore, a premarket approval application would be necessary for the device because general controls and performance standards were insufficient to provide reasonable assurance of the safety and effectiveness of the device.

We prepared for this panel meeting by reviewing all the information submitted by the sponsors in response to the 515(i) call for information.

We also had the clinical practice guidelines for the treatment of pressure ulcers, which I would like to read to

claims of product effectiveness for topical oxygen chambers are combined with studies of full body hyperbaric oxygen chambers.

In addition, wound healing is an extremely complex process. All the clinical data on topical oxygen chambers that were in studies reflect the following issues:

Often they are single case experiences or studies with a very small number of patients, less than 100.

Patient assessment is often unmasked, which opens the possibilities of bias in patient selection and assessment.

Most of the studies were uncontrolled. There are few examples of control studies, of which two probably come to mind. One is a six-patient clinical controlled study and then a second study that was done on the role of topical oxygen on MRI detection.

Finally, wound repair is a very complicated process, of which this device is only one component. Successful wound repair requires wound bed preparation, wound dressing, patient nutrition, in the case of a diabetic ulcer off-loading, or in the pressure ulcer, pressure elimination, or in the case of venous insufficiency ulcers, compression to relieve that.

Finally, patient compliance is an essential component in wound repair. Unfortunately, many of the articles did not respond to many of these components, so it is

difficult to really understand how these factors were controlled or if equivalent treatment was given to each of the patient groups.

On the last side is the question for the panel. The panel question is:

If your recommendation supports reclassification, based on all the information considered at this meeting, please discuss the special and/or general controls necessary to provide reasonable assurance of safety and effectiveness. Thank you very much.

DR. MORROW: Thank you. Are there questions for Dr. Durfer?

Okay, if not, we will start the panel deliberation portion of this meeting. Dr. Boykin, am I correct that you have some remarks to open our deliberations?

**AGENDA ITEM: Panel Deliberations.**

DR. BOYKIN: I will try to make this brief. A lot of this is very redundant. On behalf of the panel, just underscoring some comments that have been made already about the confusion between HBO and topical oxygen, I think enough has probably been said.

I wanted to focus my comments on the discussion that was presented by Dr. Heng, and I will kind of work my way into that.

Basically, HBO is responsible for increasing significantly the plasma oxygen content that provides systemic oxygen transport.

By doing this, we can achieve levels of PO<sub>2</sub> in the blood stream that are significantly elevated. At about three atmospheres, you are operating at about 1,500 millimeters of mercury for PO<sub>2</sub>.

This oxygen association curve, which we normally deal with, is on the extreme left in the graph. This is where the topical oxygen basically operates.

We also know that, for other reasons that have been cited here, that there is little information to support the fact that there is a hyper-oxia system with topical oxygen.

We have also had research in reliable animal models which showed that at normal baric conditions you have oxygen diffusion at about 64 microns in a normal capillary of the epidermis, which increases to about 250 microns under hyperbaric conditions.

It is this hyperoxia that reverses ischemic and hypoxic changes in certain conditions clinically, and allows the formation of new blood vessels.

Now, what is important, though, is that at the present time it appears that HBO has two primary mechanisms of operation.

In an oxygen mediator -- this is because of hyperoxic changes where you have improved cellular metabolism and collagen production, granulation tissue formation -- the neovascularization has been proven as a product of the oxygen gradient.

Also, you have a significant improvement in white cell microbial killing.

The other mechanism is nitric oxide production. This is research that was just completed recently by the Air Force.

It is the nitric oxide component which is responsible for the inhibition of leukocyte sticking that causes the ischemia reprofusion syndrome.

This work has been done by Zamboni in Nevada and several others, who now can point to this particular mechanism as being responsible for the reversal or ischemia reprofusion.

It also prevents the production of extravascular oxygen free radicals released by the activated mixtures of these three endothelial seams.

This production of nitric oxide, especially from the endothelial cell, cannot be duplicated by air or by oxygen at sea level.

It is imperative that the free oxygen plasma component be elevated to about 2.5 to 2.8 atmospheres.

So, we have a situation where we have some similarities in terms of mechanisms. What we can understand is that the clinically significant mechanisms of action for HBO therapy are not achieved for the topical oxygen.

That brings us to the schema that we have to deal with today. What is important for us to understand on the panel is what is the efficacy that we are dealing with in topical oxygen.

We need to know what these mechanisms are. They need to be clearly identified so that they can be studied, so that appropriate models can be structured, so that there might be a statistical data analysis done in an appropriate form, with randomized blind trials.

From this, hopefully, a risk benefit ratio and evaluation might be made for our product classification.

Unfortunately, at this time, it is very difficult for us to move through this process because of the information that we have.

There have been many instances of devices that have come before this organization in the past in which the early studies have been inconclusive or even negative but, when re-evaluated with proper controls and when we focus on different types of pathology, we can find a substantial benefit and can understand the types of conditions under which they might best

be applied.

Perhaps that is the dilemma that we have here. Maybe there is a role for topical oxygen therapy. Maybe there will be a role for it in other types of issues besides wound healing.

I believe that it would be reasonable for future studies in this area, to look at factors, well controlled, the time of healing, perhaps decrease rate of infection, which has not been looked at appropriately.

It would also be very valuable for us to understand if there is any enhancement of the positives or enabling wound healing mediators with this device, such as growth factors or nitric oxide.

I believe it might be of some value also for the manufacturers of this device to look at adjunctive studies with wound modulators such as hydrogels, growth factors and synthetic crystals.

DR. MORROW: Thank you, Dr. Boykin. Is there other general discussion from the panel at this point in time?

Hearing no general discussion from the panel, we will then move on to a specific discussion of the question in front of us, which if someone could put that back up on the overhead and turn it on, I could remember precisely what it is.

Basically, does the evidence before us justify the reclassification of this device which is currently class III.

I suppose we should start with that issue before we talk about the special or general controls, and get the sense of the panel on whether or not reclassification is appropriate at this time.

Dr. Boykin, since you have obviously given this issue considerable thought, maybe you could tell us your opinion of that question.

DR. BOYKIN: Madam Chairman, at the present time, I believe, with the information that has been presented, there is quite a bit of enthusiasm for it, but I see a significant lack of evidence that would support a reclassification

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DR. BOYKIN: Madam Chairman, at the present time, I believe, with the information that has been presented, there is quite a bit of enthusiasm for it, but I see a significant lack of evidence that would support a reclassification.

DR. MORROW: Can we hear the sense of the other panel members, please? Dr. Chang?

DR. CHANG: In reviewing the materials, I did not see significant additional information from the decision of 1988, to change the classification.

DR. WHALEN: I simply would concur with what was just said.

DR. MORROW: Dr. Burns, do you have a comment?

DR. BURNS: I also agree with those comments.

DR. MORROW: Ms. Brown Davis, anything to add here?

MS. BROWN DAVIS: No.

DR. ANDERSON: I agree, I do not see a reason to change the classification.

DR. GALANDIUK: I believe with the claims of less scarring, I don't think we saw any real objective as to why we should reclassify the device.

DR. MORROW: Dr. Witten, I think you hear a fairly unanimous feeling of the panel that sufficient new evidence regarding efficacy has not come before the panel to support reclassification of the device at this time.

Are there further questions you have for the panel at this point?

DR. WITTEN: To the specific question, I guess I would like some clarification. I have a question from Mr. Dillard.

MR. DILLARD: I think at this point we would appreciate at least going through the formality of the classification/reclassification issues.

I think that pulls together the sense that you are trying to give us, and will also give us a written kind of review of what was said.

DR. MORROW: Thank you. According to my agenda, prior to performing that function, we should have the second open public hearing.

Is there anyone in attendance from the public who has new or additional comments to bring before the panel?

Could you please reintroduce yourself for the

record?

**AGENDA ITEM: Open Public Comments.**

MR. LASLEY: Again, I am Bob Lasley, retired CEO of Stevenson Industries, which has been manufacturing chambers for 20 years.

A point that I didn't mention earlier that I think is significant is that the topological treatment costs a small fraction of what hyperbaric oxygen costs.

There is no argument on our part that hyperbaric oxygen doesn't work. It does work; we know it works, but it is very, very expensive.

Topologic will never generate additional evidence, in my judgement, will never generate additional evidence, double blind, clinical studies, something to impress you with a reasonable study of over 100 patients. It is just not going to happen.

Another point is how many are there. We have probably manufactured 2,500 to 3,000 of these portable, durable chambers. These are not disposable.

Twenty-five hundred to 3,000 is a very, very small market. That represents, I think, one chamber in every other hospital across the country. It is too small.

I don't believe, unless some benevolent benefactor decides to run these studies, I don't believe you are going to

get any real, hard-nosed evidence, clinical, statistical, proven evidence, as to how they work.

That doesn't change the fact that they do work. They do work. I guess I close by saying, if you leave them class III and call for PMAs, I think the topical oxygen will go away, because there is no way that evidence can be practically obtained. Thank you.

DR. MORROW: Thank you. Is there other public comment?

MR. WESTWOOD: Joe Westwood with TWR, manufacturer of the topical disposable process, as compared to the non-disposable product that Mr. Lasley was just discussing.

One point -- and I think this came out of the question for Dr. Myers. We do not believe that topical oxygen does increase the oxygen levels in tissue, only in the open wound tissue itself.

These tests that were done in the leg, for example, had nothing to do -- in our opinion -- with the effect of the oxygen as it is applied directly to the wound. We believe it is primarily a surface effect, we are looking at surface wound tissue.

We have tried to measure oxygen three centimeters away from the wound itself, and you find there not to be an increase in the oxygen levels, from the topical oxygen

approach.

We believe it is strictly a surface tissue phenomenon. We believe there are some good theories on the mechanisms for how it works. Dr. Heng went through her explanation. There are others perhaps, for how it works.

No one knows for sure how it works. We do know that it works; there is no question that it works. It has been demonstrated many, many times that it does.

How it works, we don't know yet. That will require further studies, further tests. One thing I agree with is do not look at TCOT in the leg as an indication of what effect topical oxygen has on the wound, because it has nothing to do with that.

We do not suggest that topical oxygen will increase blood oxygen levels or non-tissue wound oxygen levels at all.

DR. MORROW: Thank you. Is there additional public comment?

Dr. Heng, I thought I heard earlier that you had a brief response to the discussion that came after your presentation.

DR. HENG: I just wanted to point out the fact that until you use it exactly right, too little is just the same as too much. If you don't have enough oxygen, you will not get ATP. If you have too much oxygen, with the oxygen toxicity,

you will still end up with no ATP.

I just wanted to ask Dr. Myers a question. When you did your low Topox study, what was the partial pressure of the oxygen in the Topox chamber?

DR. MYERS: We followed the directions of the manufacturer to the letter. We had a representative of the --

DR. HENG: Fifteen millimeters?

DR. MYERS: -- to come out and show us how to use it. It had been used in the rehab hospital for two years before that, but we reiterated the trial, asking him to show us exactly how to use it, and then we followed his directions.

DR. HENG: Because 50 millimeters of mercury using Topox is far too high. We found that even 25 would generate oxygen toxicity. Ours is much lower.

The other thing is, anything more than one atmosphere is hyperbaric. Thank you.

DR. MORROW: If there is no further discussion from the panel --

**AGENDA ITEM: Concluding Panel Deliberations:  
Completion of the Classification Questionnaire and  
Supplemental Data Sheet and Vote.**

DR. WHALEN: I may be out of order and please tell me if so. Before we get into this form, I have a question about the form that I would like to ask.

DR. MORROW: Fire when ready.

DR. WHALEN: If one looks at questions six and seven on this form, we read it 15 times. If you answer no, it looks to me like the question six and seven are exactly the same.

If you answer no in question six, reclassify into class I, it is the same question in question seven, if you answer no, you classify it in class III. What am I missing?

DR. MORROW: You don't necessarily go there. There are different antecedents to those questions, as I read the form.

Like, you only go to seven if you answer yes to one, two or three, whereas you go to six if you answered no to all those things.

I think we have already made that jump, but we can ask our expert from the FDA.

DR. WHALEN: If you answer yes to six, you must answer yes to seven, because it is the same question. The question ends with a question mark, and the rest is amplification in seven.

DR. MORROW: You kind of lost me. Would you like to clarify this for us?

MR. DILLARD: The point you are trying to make, Dr. Morrow, is correct. How you get to that question does have an impact here.

The reason it has an impact here is something we talked about this morning. It is a not utilized piece of the statute, that the answer to question six specifically targets.

That is, if a product, if you work down through the sheet, and virtually what you are saying that the product is such low risk or almost low risk as a product -- and you answered no to all the questions on the right-hand side -- but there are really no special controls that could be established on the product, there is one part of the statute -- in section 515, I believe -- that talks about the ability to classify a product as class I because the risk is so low, even though you are unsure about how to control for, or even the necessity to control for those risks, that you could, in effect, classify a product in class I.

That is what that specific question gets to. It is only because it is so low risk that you can even get to that question.

It is a piece of the statute that I don't think has ever been used, to be quite honest. We have never said, this is so low risk, or no risk, and you can't even contemplate the idea of controls that it could be at the lowest classification category of class I.

It is a concept that is a little bit difficult to understand and actually has not been utilized.

I see how it is raising confusion in your mind, how you can have such dichotomy in a device, that you can't develop special controls, that it could be class I but it could also be class III.

It is really based on whether or not there is any risk at all associated with the product.

DR. CHANG: This may be out of order, because it is not dealing with efficacy, but the question to Mr. Dillard, since we are talking about risk, in general, the higher the class, we tend to look at a higher category.

I would like to know, as we compare, say, topical oxygen which is not hyperbaric in the traditional sense, where hyperbaric does have potential systemic side or organ complications, how does the rationale -- although this is not the question -- how is hyperbaric full body chamber class II?

MR. DILLARD: This is going to be difficult and I hate to go on about this. Of course, part of the classification, it isn't only technically a risk based classification system.

We are factoring in the risk benefit ratio associated with the products, and the potential benefits or the known benefits versus those known risks.

I think in the case of hyperbaric oxygen, it has been a number of years since I have looked at the transcripts,

when they were classified, but I think those risks were considered real risks, perhaps even higher, if you were to compare them.

I don't know how comparable they are, but if you did some sort of comparison between topical versus the HBO chambers, yes, hyperbaric oxygen chambers may have a little bit higher risk associated with them.

I think also there were demonstrable benefits associated with the use of hyperbaric oxygen also. When one factored in the risk benefit ratio associated with treatments with full body hyperbaric oxygen, and that if you looked at them as risks, there were clearly identified special controls -- at the time they were performance standards, but now it is special controls -- to control for those risks, such as looking at national fire prevention standards, in terms of increased oxygen, and the flammability of oxygen, and some other electrical kinds of standards.

There were some things specifically targeted that the panel at the time -- which was the anesthesiology panel -- thought controlled for those risks that were identified.

It was also the fact that there were the demonstrable benefits, and the demonstrable effectiveness that helped outweigh those potential risks, which may be higher in hyperbaric oxygen, but led them to a recommendation of class

II and led us to believe that we could use special controls to control for those risks.

I think that is the issue here, and I think the one that is before you. The risks, given just looking at topical oxygen therapy, that the risks may be a little bit lower in the sense of comparability to hyperbaric oxygen, but does the effectiveness data, or do the benefits associated with the therapy outweigh the risks and are they something that is demonstrable.

I think that is the issue that you are struggling with here, in terms of whether or not there is enough information to reclassify.

DR. MORROW: Thank you. Is there other discussion from the panel at this moment? Then if I may refocus, in polling you all, you just said that you did not feel that reclassification was indicated because of efficacy data.

We are now charged with filling out this sheet to reflect in more detail that particular thought.

So, item number one, is the device life sustaining or life supporting?

DR. ANDERSON: No.

DR. MORROW: No. Any disagreement with that?

Is the device for a use which is of substantial importance in preventing impairment in human health.

DR. ANDERSON: Yes, it is. The question here, as I am reading this -- correct me if I am wrong -- is the problem which this is trying to address, which is these ulcers, are those of substantial importance, and do they prevent -- the reason that this is important is because if the answer to all three of these is no, then this is not either class II or class III. That would force us into class I.

DR. MORROW: Remember, we are now at reclassification rather than classification. What we were doing this morning is not absolutely translatable into this.

As I would interpret that, that is not necessarily a true statement, what you just said.

DR. ANDERSON: Can you clarify it for me? Is not the question, is this a significant problem, in terms of human health, or is it not.

MR. DILLARD: We are focusing on question two here. I think maybe the best that I could do under these circumstances is to help clarify the way in which you are looking at question two. Let me see if I can get you something here.

It says, is the device for a use which is of substantial importance in preventing impairment of human health.

I think as we have noted before, that can be broadly

interpreted. I think Dr. Anderson, the way in which you are trying to address that issue of saying whether or not the types of wounds that you are considering here, and whether or not this therapy applied to those wounds would be important or would have an effect in the impairment of human health, if that type of wound is important to human health, then I think you can broadly interpret that issue either way you wish to interpret it, either by saying that the device is important because it is of substantial importance that the wound could impair human health, or no, you don't think the therapy has much effect in the overall management of that wound.

DR. ANDERSON: In this particular case -- and I am going to state my ground on this point -- the question isn't, is the device of substantial importance. The question is, is the device for a use which is of substantial importance.

The manufacturers we have just heard from are saying that this is for use on these ulcers. These are a significant problem in health care.

We have also said that we do not believe that this should be reclassified from a class III. If you carefully look at how this was laid out, you can see how, if this was in fact for a treatment of an unimportant problem, then a no, no, no would put this as a class I.

DR. MORROW: I think this form doesn't apply to this

discussion. Is there further discussion from other panel members about their response to item two?

DR. WHALEN: Yes, I am going to agree with him, based on the analysis he has given. We are not talking about the device per se, we are talking about the condition itself.

DR. MORROW: Other discussion?

DR. GALANDIUK: This is not consistent with what we did this morning. If it was a dressing for a burn, then it was an important issue, but if we go along with what we did this morning, this is not consistent.

DR. BURNS: Is there a difference when you are talking about a product claim for improving wound healing. Before we were addressing products that are covering a wound.

DR. ANDERSON: You are also talking about a classification system. Here we are talking about the actual application of a product.

DR. WHALEN: The only thing I would say there is some inconsistency in this area.

DR. CHANG: I will say no, because that is what I believe.

DR. MORROW: Dr. Boykin, can you voice an opinion on this?

DR. BOYKIN: I would say yes, for the planned indication.

DR. MORROW: Okay, does the device present a potential unreasonable risk of illness or injury?

DR. GALANDIUK: No.

DR. ANDERSON: No.

DR. MORROW: All right, we are now on item number six. Is there sufficient information to establish special controls to provide reasonable assurance of safety and effectiveness?

MR. DILLARD: I would just like some clarification as to did you reach a consensus on number two, or a direction on number two?

DR. MORROW: We reached a direction on number two. The vote was three to two, that the answer was yes.

MR. DILLARD: So, from the standpoint of the next steps, the working premise is that we answered yes. Okay.

DR. MORROW: Number four is did you answer yes to any of these questions. I said yes.

The next question is, is there sufficient information to establish special controls to provide reasonable assurance of safety and effectiveness.

DR. WHALEN: Madam Chair, just a question, since the question you read is both six and seven. Are you reading number six or number seven?

DR. MORROW: I am reading it as seven.

DR. WHALEN: I say no, there is not adequate information regarding safety and effectiveness.

DR. MORROW: Other discussion?

DR. BOYKIN: I would agree on the effectiveness also.

DR. GALANDIUK: I would add that we need more information on randomized controlled trial, or more information specifically about the current trial, to establish efficacy.

DR. MORROW: Other comments, Dr. Chang, Dr. Boykin?

DR. CHANG: No.

DR. BOYKIN: No comment.

DR. MORROW: So, the answer to that question is no. All right, item number 8. If a regulatory performance standard is needed to provide reasonable assurance of the safety and effectiveness of a class II or III device, identify the priority for establishing such a standard.

Do you want us to answer the question?

MR. DILLARD: Yes, please.

DR. MORROW: In other words, by prioritizing this, we are doing what we discussed earlier in the day regarding the priority for calling for PMAs. Is that where we are?

MR. DILLARD: This is actually asking you whether or not, as we spoke about earlier today, you believe a regulatory

performance standard, a federally mandated performance standard, is necessary to provide the types of assurance of safety and effectiveness, before this product or individual products under this category should go to market.

If you believe that a federally mandated performance standard is necessary, then we ask you for a priority.

It may be that you believe because your recommendation that the product stays a class III device, that you don't necessarily need a performance standard. You only need a PMA to look at this device.

If that is the case, that is how other panels have interpreted it, you could say, well, it is not applicable; we don't think you need to develop a performance standard; we think you need to take a look at the PMA.

DR. GALANDIUK: Could you define federal performance standards.

MR. DILLARD: A federally mandated performance standard is one that we would actually go through the development process of proposing a standard, asking for comments and then finalizing the standard, the same sort of thing we will have to go through to call for PMAs for this product, if that is the way they end up.

The performance standard would identify either some risk or some effectiveness criteria for information that the

FDA would then walk through and say, if you did a certain number of tests, or if you did these things, or if they passed these criteria, then the product would meet that standard.

It doesn't necessarily say that the standard would be approved, but it would say that it meets that particular standard.

As I mentioned, perhaps in training this morning, one of the reasons -- there haven't been very many -- performance standards that we have published had to do with cables and leads.

It was more of an issue of plugging male connectors into AC outlets in a hospital, and having adverse patient outcomes, obviously, by doing that.

So, there was a performance standard that we put forth that said, manufacturers need to come in and tell us how they are going to address that problem of not having male connectors that would then be able to be plugged into AC wall outlets.

That was one. We said, everybody who has those kinds of connectors has to come in and they have to meet certain criteria. That is just an example in terms of the context of what we are talking about regarding a performance standard.

DR. MORROW: So, regarding the general question,

first of all, of making a performance standard -- Dr. Galandiuk, do you have a comment?

DR. GALANDIUK: I just had one question to Mr. Dillard in regard to cost to manufacturer. If you had a performance standard, that you show us the next 100 that you build, does that mean that they would also have to make a PMA?

MR. DILLARD: Not in this case, it cannot. What you are saying is that there needs to be, then, a prospective trial to determine safety and effectiveness for each individual product.

That being the case, it still would be a class III device, at least by what you are recommending here. Those would be requirements that you believe would need to be met in order to then submit a PMA and get approval for the product, which would be, as I said, in general it is very uncommon and I don't think it has ever happened for a class III PMA product, to have a performance standard.

DR. MORROW: To get back to the performance standard issue, comments from the panel regarding this? Do they feel that a performance standard is indicated here or is this not applicable to this particular device?

DR. WHALEN: Not at this time.

DR. MORROW: Other discussion?

Moving to item 10, now we come to advice recommended

for the classification or reclassification into class III, identify the priority for requiring premarket approval submission applications, low priority, medium priority, high priority. Discussion on how urgent the need for this to happen, I guess, is what we are talking about.

I think in this context we might consider that the issue here is not safety but efficacy.

DR. ANDERSON: We heard one of the manufacturers this afternoon say that he is concerned about, by virtue of these regulations, that this product is going to go away.

We have also heard from one of our own experts that maybe there is a potential for this. The problem is that the good studies haven't been done.

We don't wish to destroy a product that might have some efficacy, were these studies done. If I am understanding this correctly, if we make this a low priority, then there is less pressure on the manufacturer to spend extra money on paperwork, and it might provide more opportunity for them to do the studies that do need to be done. Is that a correct interpretation?

MR. DILLARD: I might characterize it a little bit differently. I think what you would be placing is in terms of a priority to FDA to call for PMAs for on the product.

I think it doesn't impact necessarily exactly the

manufacturers in the way in which you characterized it.

I think what one of the interpretations might be is that if you place a low priority on calling for PMAs on this, that it may afford the opportunity -- and we are certainly trying to do this for manufacturers of class III pre-amendment devices where we are calling for PMAs, where effectiveness is the issue -- to work with manufacturers to try to develop the kind of data that would either answer the question that the products are effective under a PMA, or we would develop the right kind of data set in general across the product category to say, now there is enough information to reclassify the product.

I think a low priority assigned to that will afford the agency a little bit more time in which to do that, and it may be beneficial to the manufacturers in developing it, yes.

DR. GALANDIUK: One more question. Before, Dr. Burkhardt mentioned that there would be a certain period of time, if this was not reclassified, during which time the manufacturers can submit PMAs. What is that time exactly?

MR. DILLARD: I will try to spend two minutes and quickly go through what the process would be.

After we would propose to call for the PMAs, there would be a comment period. The manufacturers can comment on it. Usually they are 90 days.

We would look at the comments, we would analyze the comments. If we still believe it should be a PMA device, we would go final with that call for PMAs.

Ninety days after that final rule would publish, declaring that all these kinds of products need to come in with a PMA, 90 days after that date, there has to be a PMA submitted from that manufacturer, or that product has to come off the market, as of that date, 90 days after that final rule.

If the manufacturer submits a PMA application, it will undergo a filing review. Forty-five days after that, or before, we will make the decision whether or not that PMA should be filed and should undergo a substantive review.

Any product that would not be filed because it was incomplete administratively, that product would also, too, have to come off the market at the time of a non-file-able decision.

Once a PMA is filed, it will undergo the customary scientific review. I am sure we will hold a panel meeting, as we have for many PMAs, to get panel input on that specific device.

We need to, and must, on class III pre-amendments devices that we call for PMAs on, make a decision in 180 days.

We will make a decision on that product in 180 days.

If we don't, the product has to come off the market. That is the impact. So, there is added pressure, I think, for us to act on those devices in 180 days.

If the manufacturer has a product, and they have submitted within 90 days, it is filed, it undergoes the review, throughout that whole time, before the final decision, they can continue to market the product, as long as they are meeting those other regulatory requirements.

The other way that they could continue to have the product available at the time for the call for PMAs, is to submit an IDE application. It would be under study at that time, and then they could be distributing the product for the purposes of investigational purposes only.

That is really the outcome of calling for PMAs and the various steps the manufacturer has to go through.

DR. MORROW: Is there a recommendation from the panel on the priority for PMA submission?

DR. ANDERSON: I recommend a low priority.

DR. MORROW: Discussion? Disagreement?

DR. GALANDIUK: I agree with Dr. Anderson, that cost wise and availability wise, the device is a lot better than a hyperbaric oxygen machine. I would really like to see 'devices' that we call for PMAs on, make a decision in 180 days.

We will make a decision on that product in 180 days.

data that there is some efficacy.

DR. MORROW: Further discussion? Okay, item number 11a. Can there otherwise be reasonable assurance of the safety and effectiveness of this device without restrictions on its sale, distribution or use because of the potential for harmful effects, or collateral measures necessary for the device's use.

DR. GALANDIUK: No.

DR. MORROW: We have a no. Is there disagreement with that?

Finally, number 11b, identify the needed restrictions. The first of these is that it can only be prescribed upon the written or oral authorization of a licensed practitioner. Is there agreement with that?

Is there a need for further restriction to use only by persons with specialized training and experience above and beyond that obtained by having a license?

DR. ANDERSON: No.

DR. MORROW: We have a no. Is there disagreement with that?

Is there a need to restrict this use to certain facilities?

DR. ANDERSON: No.

DR. MORROW: No. All right, we will now move on to

the supplemental data sheet. Is this device an implant?

Are there any specific items that need to be considered in labeling here? Hearing nothing for the label.

Is there a concern about risks to health presented by the device?

DR. GALANDIUK: It was mentioned before that it could adversely affect circulation to the extremities.

DR. MORROW: Is there consensus that there is concern about the circulation to the extremity that we need to list on this form? Is that something you are raising for consideration for listing?

DR. ANDERSON: Our putting it on this form just means the FDA has to consider that in their final recommendation?

DR. MORROW: That is correct.

DR. ANDERSON: I agree with the recommendation.

DR. MORROW: Other discussion?

The recommended classification of the panel was to retain class III classification, and the priority issue for class II or class III was low from our previous work sheet.

We can move to number 8, the summary of the information upon which we base this classification recommendation.

It is my sense of the panel that the major concern

here was the lack of convincing data of efficacy.

Although we have listed this possible concern about health risks, we have not been presented with any data that indicates risk with the clinical use of this device. Is there anything that people would like to add to that summary statement?

Okay, we have identified as restrictions on the use of the device that it needs to be prescribed by a licensed practitioner.

We do not need to do item number 10.

Item number 11, regarding existing standards applicable to the device, components, parts and accessories. Are there any comments that need to be appended in this area?

Hearing none, I think we have filled out the form. We now need a motion to accept the classification work sheet as filled out, with a recommendation of maintaining class III for topical hyperbaric oxygen chambers.

DR. WHALEN: So move.

DR. MORROW: Is there a second?

DR. BOYKIN: Second.

DR. MORROW: It has been moved and seconded that topical hyperbaric oxygen chambers will be classified as class III devices. I am now going to ask each of the panel members to vote and state their reason for so voting. Dr. Anderson?

DR. ANDERSON: I vote for keeping this in class III because of lack of data demonstrating efficacy of the product.

DR. GALANDIUK: Same thing.

DR. CHANG: Vote to approve the motion based on the same reasons.

DR. BOYKIN: Same reasons.

DR. WHALEN: For the same reasons.

DR. MORROW: Dr. Witten, it is the unanimous recommendation of the panel that topical hyperbaric oxygen chambers be classified as class III devices. Do you have other questions for us on this matter?

DR. WITTEN: No, thank you.

DR. MORROW: I believe the final piece of business before the panel today is to select meeting dates for our next series of meetings.

There is the potential need for a meeting in the late January or February time frame. Apparently, based on discussion of the panel, the preferred date for that is in the February 3 vicinity, pending the availability of the materials for review and conflicts within the FDA.

In addition to that, we have a tentatively scheduled panel meeting for June 16-18, 1999, possibly August 19-20, 1999, pending the availability of submissions and, again,

November 15-16, 1999.

Other comments or discussion regarding that?

PARTICIPANT: Will people who signed up for this meeting be notified of subsequent meetings?

MR. DILLARD: I think the question from the audience is, will the general public be notified about meeting times and the availability.

The answer to that is yes. We try to do that on a regular basis. We have a hot line that can be called up.

We announce well in advance the panel dates and times, as well as the web site and the Federal Register where we announce panel meetings. Yes, in the future, the public will know about them.

DR. MORROW: If there is no other business, I would like to thank the panel for their participation in today's deliberations.

DR. WITTEN: I would like to thank the panel, the public and the FDA. In particular, I would like to thank Hany Demian for taking over the exec sec role on short notice.

MR. DEMIAN: At this time, I would like to say any materials that you would like to leave with us for us to take care of, just leave it in front of you and I will pick it up and I will take care of it.

I would like to reiterate, thank you very much for

all of you help. We do appreciate it. The meeting is adjourned.

[Whereupon, at 4:10 p.m., the meeting was adjourned.]