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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

PUBLIC HEARING
COMBINATION PRODUCTS CONTAINING
LIVE CELLULAR COMPONENTS

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P A R T I C I P A N T S

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P R O C E E D I N G S**Opening Remarks**

MR. BARNETT: I would like to welcome you to this public hearing on FDA's regulations of combination products containing live cellular components. I am Mark Barnett, with the FDA, and I will be serving as your moderator today.

With me on the panel are Dr. Mac Lumpkin-- I am going to ask you, guys, to wave your hand a little bit because we can't see the name cards in the back. Dr. Mac Lumpkin, FDA's Senior Associate Commissioner for International Activities and Strategic Initiatives; Dr. David Feigal, Director of FDA's Center for Devices and Radiological Health; Dr. Kathy Zoon, Director of FDA's Center for Biologics Evaluation and Research; Kate Cook, an Associate Chief Counsel who has been actively involved in jurisdictional issues; and Suzanne O'Shea, the jurisdiction expert in the Office of the Ombudsman.

Let me first briefly describe the issues we are going to be talking about today, and then

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let you know about the format we are going to use for the meeting. The products we are going to be talking about at this meeting, which are used to promote wound healing, consist of living human cells that are combined with a device matrix. It is this combination of components that leads to the questions that are on the table because, although living human cells are biologics, the matrix with which they are combined is a medical device. And, so the first question is essentially about product assignment: Should these particular combination products be regulated by FDA's Center for Biologics Evaluation and Research, or by FDA's Center for Devices and Radiological Health?

So far, many of them have been regulated by the Center for Devices and Radiological Health. So, to refine the question a bit, it really boils down to whether this regulatory responsibility for some, or all, of these products should be shifted to the Center for Biologics Evaluation and Research.

How does FDA decide in a case like this?

Well, the law says that the key factor is the product's primary mode of action, and I am sure some of you are going to be making comments on your views about this today.

Beyond the issue then of who within FDA regulates these devices, a second essential question concerns how they are going to be regulated to ensure adequate and consistent regulatory oversight. We are interested in your thoughts about that, and also about what the public health concerns may be with these products, and what information should be required in order to get premarket approval. Speaking of premarket approval, irrespective of which center does the regulating of these products, should they be subject to the PMA process or the BLA process?

To help us answer these questions, we set up this public hearing to solicit the views of various stakeholders, researchers, clinicians, professional groups, trade groups, manufacturers and consumers.

Here is how we have organized the meeting

to get that information. In the Federal Register announcement on May 15th, we asked interested organizations and individuals to register to speak at today's meeting, and we asked them to address three sets of key questions, and those are laid out pretty clearly in the Federal Register announcement which should be in the packet that you received this morning.

Essentially, the first set of three questions addressed potential public health concerns with these products, including information that should be required for premarket submissions, and also manufacturing controls.

The second set of questions dealt with how FDA should determine the primary mode of action of these products.

The third set of questions asked what other factors FDA might consider in answering this jurisdictional question if, in fact, the agency could not conclusively determine what the mode of action was.

Sixteen people signed up to speak today

and help answer those questions, and we will hear from them first. When that is done, we will open the floor to anyone else who may wish to address these questions. Notice, I said "these questions" because, in fact, we are not going to discuss other kinds of products today. Again, our discussion will be limited to those combination products consisting of living human cells and a device matrix that are used for wound healing. Those are the limitations of what we are talking about today.

Let me say a few words about time. If you are a scheduled speaker, the duration of your presentation, as it is shown on your agenda, is based on the time you told us that you would need, but in no case is it any longer than 20 minutes. We had to set a 20-minute limit in order that everyone can get a chance to speak, not just those who signed up but those who may want to speak afterwards. So, please, I am going to ask you to stay within the allotted time, and I am going to help you do that by giving you a gentle warning when you have two minutes left and then asking you

to stop when it is over.

Well, that is the game plan for today's meeting. Before we go on, let me stress that this is essentially a listening exercise for the FDA. We really want to hear what you have to say on these issues, and our span of attention is going to go beyond today. We are having this meeting transcribed, and the folks on the panel and their staffs are going to pay careful attention to what they read in those transcripts as they decide what to do about this issue. This is not your last chance to comment. The docket will stay open for written comments until August 23rd.

One more housekeeping thing, we need a copy of your presentation if you are a scheduled speaker. Please, leave it at the registration desk before you leave.

So, before we begin and call on our first speaker, let me ask Dr. Lumpkin to give us some welcoming remarks on behalf of the agency. Mac?

Welcoming Remarks

DR. LUMPKIN: Thank you, Mark. Good

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morning, everybody. I am Murray Lumpkin, and I am here today in my capacity as Dr. Crawford's deputy. On behalf of Dr. Crawford and the entire senior leadership team at FDA, I would like to, again, welcome each of you for being here and express our sincere thanks to each of you for taking time out of your schedules to come and be with us today and offer your perspective and your insights on this particular issue.

This is obviously a very difficult issue for us. If it wasn't, we wouldn't be here today. So, it is a very important meeting for us. This is a very important part of our decision-making process and I, and I know all of my colleagues here at the table, look forward very much to hearing what you have to say today and in the days and weeks to come as we proceed to make our decisions on these very, very important products.

Again, on behalf of Dr. Crawford, welcome and thank you for being here today. I look forward to hearing from you. Thanks, Mark.

MR. BARNETT: Our first speaker is from

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the U.S. Pharmacopeia, Dr. Sally Seaver and Dr. Ian DeVeau.

United States Pharmacopeia

DR. SEAVER: I am Sally Seaver and I will be the speaker for USP.

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I would like to thank the Office of Ombudsman at the FDA for the opportunity to speak at this meeting. I am speaking today in my role as Chair of the United States Pharmacopeia's Expert Committee on Gene Therapy, Cell Therapy, and Tissue Engineering. This presentation is based on this committee's past work, which culminated in the information chapter 1046, "Cell and Gene Therapy Products;" its current work on an information chapter on "Ancillary Products for Cell and Gene Therapy Products;" and its work with companies in writing monographs for wound healing products that contain live cells.

It is not the committee's intention, my expert committee's intention today to testify as to which center in the FDA should have jurisdiction

over these products or on the primary mechanism of action of these products. Our work has always assumed that reproducibility in manufacturing a safe product with live, functioning cells was the goal. I intend to focus today on our work to provide information for cell and gene therapy products in general, and monographs and reference standards for wound healing products with live cells in particular.

The forerunner of this expert committee was an advisory group to the USP Subcommittee on Biotechnology and Gene Therapy that was formed in December, 1997. The group was composed of scientists and clinicians from academic medical centers, the biopharmaceutical industry, both large and small, and the government, including the FDA. The members have experience with cell-based products for wound healing, bone marrow transplantation, xenogeneic cell therapies, patient-specific cell therapies, and viral and non-viral gene therapies, as well as traditional biotechnology-derived products.

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At the December, 1997 meeting the group decided that we would write an informational chapter on cell and gene therapies, after which we could focus work on the issue of ancillary products for these cell and gene therapy products. The goal of this first chapter, 1046, "Cell and Gene Therapy Products," was, and I quote from the chapter, to summarize the issues and best current practices in the manufacturing, testing and administration of cell and gene therapy products, end quote. In other words, we wanted the chapter to contain all the information the committee would have liked to have known if they were starting out in the field today. We wanted the chapter to cite examples that are directly relevant to those making cell and gene therapy products. We wanted to look forward towards the standards and practices for approved products, since there were only a few approved at that time, but we wanted to present also general information on the development, manufacturing and testing of these products.

Since this is a new field, we considered

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the relevance of all regulatory guidances and whether or not they specifically were devised for these products. These included the numerous CBER points to consider and guidances, the ICH guidelines, especially those for biotechnology-derived products, 21 CFR 210, 211, the 600 series and the 820 series, especially the Quality Systems Regulations, and ISO guidances. We looked at them all.

We were influenced by aspects from all of these sources. In fact, an overriding theme of the chapter is that the ICH guidelines, especially those for biotechnology-derived products, are useful in that the principles of these guidelines can be applied to cell and gene therapy products even if the guideline specifically states that they are not applicable to cell and gene therapy. To help apply these important principles of these guidelines, guidances and regulations, the panel tried to provide useful examples that are specific to cell and gene therapy. The goal with these examples is to go beyond the FDA definitions and

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guidances to make these guidances relevant to the field of cell and gene therapy.

[Slide]

The outline for 1046--there are actually a few copies on the registration desk out there. If we run out, please feel free to give me or Ian a call; we can send you a copy of these slides. I am going to only outline the sections that are relevant to wound healing products, and we are also going to submit to the docket a complete published copy of this chapter.

[Slide]

The first section is a manufacturing overview. In fact, we divided manufacturing into three sections. In the overview we discuss raw materials sourcing and qualification, characterization of cell and virus banks, in-process controls, specifications and validation. This section was strongly influenced by the risk assessment and design approaches of QSR and by the numerous CBER points to consider and guidances on testing these products for adventitious agents.

The manufacturing of cell therapy products section contains much information that is directly relevant to this type of wound healing product, including--at the very bottom, last but not least--some specific words for products combined with biocompatible matrices. In there, there are a whole couple of paragraphs on matrices for wound healing products.

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We felt that any preparation of the final product done at the clinical site should be viewed as an extension of manufacturing and should be supported by appropriate SOPs and facilities and by people trained in processing. That is outlined in this section on on-site preparation and administration.

[Slide]

We organized analytical methodologies so that safety was the first consideration and not last, as we traditionally see in many discussions. In addition, products need assays for defining the dose, defining potency, purity and identity.

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The stability section points out that brief excursions in temperature to outside the stated limits, such as may occur in an airplane hold or in a surgical suite, may be as damaging as long-term exposure to conditions just outside storage specifications.

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The storage and shipping section discussed issues both with storing a product frozen, as well as with shipping it in an unfrozen form.

This chapter concludes with a brief section on labeling; regulation standards and new methodologies and, yes, we call for them; a definition of terms and a list of abbreviations.

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An initial draft of 1046 was published in the January-February, 2000 issue of Pharmacopeial Forum for public comments. About 500 copies were also distributed to interested parties, mainly those people working in the field. A revised version was published in the January-February, 2001

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issue of Pharmacopeial Forum. Based on a few additional comments, a final version of 1046 was approved by the expert committee and published as part of the "First Supplement" to USP 25/NF 20, which became effective April 1st of this year.

In 2000, the expert committee also started work on a second information chapter that discusses sourcing and qualifying ancillary products for use in the manufacturing of cell and gene therapy products. Ancillary products are those materials used in the manufacture of the therapeutic products that are not intended to be in the final product. Again, the committee has found CBER's extensive guidances on adventitious agents and handling of biotechnology-derived products to be important. We also find the CDRH's QSR approach extremely helpful. The QSR spells out a more comprehensive approach to quality than CBER's specifications for the quality function. QSR starts right at the conceptualization, design and development phases with design controls, and directly addresses risk assessment for products and raw materials.

Addressing these issues up front is important for developing a manufacturing process to produce safe cell and gene therapy products that consistently demonstrate the expected activity.

More recently, the expert committee has worked with three companies on monographs for wound healing products containing live cells. A draft monograph for one of these products was published in the November-December, 2001 issue of Pharmacopeial Forum. The two other monographs are still in an early development stage. Each monograph contains sections that describe (a) the product configuration, adventitious agents and other non-USP specified testing; (b) packaging and storage; (c) labeling; (d) USP reference standard; and (e) tests to identify the product.

The committee would like to emphasize that in the USP tradition these tests are not intended to be routine release tests for the products, but are a set of tests that can be used to distinguish these cellular products from each other, from other wound healing products, and that would ensure the

consistent quality of these products. The three wound healing products we are dealing with are clearly different from each other.

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After working on its first monograph, the committee decided that monographs for wound healing products containing live cells should include the following four types of tests which are listed on this slide.

First, there should be a detailed histology of the product that clearly demonstrates the organization of the different cell types relative to the matrix, as well as the gross structural properties of the matrix. Tests to identify different types of cells that are in the product, as well as the matrix. Tests to show the cells to be viable or to have the expected metabolic activity in the final product. Finally, any other unique properties, if relevant. For instance, in the draft monograph published last fall, there is an assay that demonstrates that the top layer of this particular wound healing product

with live cells was cornified.

The reference standard for that monograph is a series of photomicrographs of the histology of the product that depict product that passes these monograph specifications, as well as product that fails these specification. These photomicrographs are in the process of being reviewed by independent pathologists for their acceptability as a reference standard.

The committee urges that all wound healing products with live cells be reviewed by the same FDA center so there is consistency of review. The committee members urge that the chosen center be versed in both relevant issues with live cell products, as well as those issues with biomaterials and their sourcing, and with ancillary products needed to make these cell products. So, three things: live cells, the matrix and the ancillary products.

They also feel that if center jurisdiction changes, there should be no undue regulatory burden placed on the manufacturers of wound healing

products already on the market as it is the committee's perception that there have been no major safety issues with these approved products.

Finally, the committee thanks both CBER and CDRH for the good relationships it has with them, and looks forward to working with whatever center is chosen to regulate wound healing products with live cellular components. Thank you.

MR. BARNETT: Thank you, Dr. Seaver, and your timing was impeccable.

DR. SEAVER: Are there any questions? I would be happy to address questions. As I said, there are a few copies of this presentation out there, and a complete copy of the chapter will actually be submitted to the docket.

MR. BARNETT: Thank you. Our next speaker is Mr. Robert Nerem, from the Georgia Institute of Technology. Mr. Nerem?

Georgia Institute of Technology

MR. NEREM: I appreciate this opportunity to make some comments this morning.

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My name is Bob Nerem. I am from Georgia Tech. I am director of the Georgia Tech Emory Center for engineering of living tissues. I am also a member of the FDA Science Board. Through that experience, I have tremendous respect for the efforts being made by FDA. I did chair the CDRH External Science Review Committee.

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I hope my comments are of some help. I thought I would start out by just placing tissue engineering in perspective. I realize we are talking about wound healing products, but obviously what we decide as a result of today and further input will have a broader impact. I think we need to recognize that this is an emerging technology with enormous potential to help patients. At the last count, 66 companies, 3000 employees but only four products approved by FDA. That is an industry that I characterize as being in a fledgling state, some would say a fragile state.

I thought it was very appropriate when Mike was talking to me about his laptop, he said,

well, you know, we are having problems with it; it is bleeding red. In fact, this industry is bleeding red. So, I think it is probably very appropriate.

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Obviously, the challenge for all of us, whether we are in the industrial community, FDA or the research community, is to define a regulatory pathway and process that will not only protect patients but, at the same time, really accelerate bringing these products and repair strategies to the market, and by bringing them to the market, to patients in the least burdensome way.

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When I chaired the CDRH 2001 External Science Review, one of our recommendations was that these kinds of products needed to be regulated with an approach which is least burdensome, predictable, timely, flexible, transparent and effective, but I go back and underline the words "least burdensome." I think that is a key issue if we are to really move forward.

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Recently we, at Georgia Tech, hosted a meeting of the Medical Technology Leadership Forum. The focus was on defining a regulatory process for combination products, with tissue-engineered products being used as an example. It was held in April and brought together the FDA, the industry and the research community. Two of the panel members, Kathy Zoon and David Feigal, were at the meeting, as well as other FDA people. The result was a series of recommendations aimed at the FDA and the community working together.

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This slide actually gives the preliminary recommendations, but I don't think we need to go into them in any detail. I think what is going to come out of that is really recommendations on a process. I think there is a feeling by many in the community that we have only begun the dialogue and, in that sense, it may be inappropriate to act too quickly on the kind of proposal that is before us today; that there needs to be a further dialogue, a

continuing of working together.

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Even though I, myself, use the words "combination products" I am beginning to wonder if, in fact, that is a misnomer because the kind of products we are talking about are not simply a combination of, for example, a biologic and a device. In fact, these products are not simple at all, and they are certainly not simply combinations, and I will come back to that theme later in my presentation. What we are talking about are integrated products that need to be evaluated in an integrated sense and, certainly, these products are representative of the kind we will see increasingly in the 21st century.

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Let me talk about two examples which may help focus at least some discussion. Let's talk about a platform technology where the first generation is simply a scaffold; the second generation is a scaffold with a growth factor or a chemotactic factor; the third generation, a cell-

seeded scaffold. This could be a wound healing product, it could be a different kind of product.

The issue here is, you know, at what point does this, in fact, move in jurisdiction? I would assume that a first generation product, if it is a wound healing product, could be regulated under CDRH. The proposal would have the third generation product regulated as a biologic. But I think it is going to be really an impediment to industry if, as a product evolves and goes through several generations, in fact, at some point it is going to transfer from the jurisdiction of one part of FDA to another part of FDA.

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The second example, and I realize we are supposed to be talking about wound healing products but I still think what happens out of all these deliberations will have a broader impact, so, I would like to talk about tissue-engineered cartilage as an example. This is really an evolution of my first example. Here we are talking about a chondrocyte-seeded scaffold. The main role

is structural. Cells are not important to the initial function, but may be important in maintaining long-term function and structural integrity. How do you evaluate such a product? That is clearly the issue.

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Certainly, in the wound healing area FDA historically has had these products in CDRH. As has already been noted, historically it has looked at the primary mode of action or function of the product, not its component parts. Certainly, in an integrated product it is very difficult to determine the contribution of each component. In that sense, it seems to be inappropriate to assign jurisdiction based on considering only one of the components, the cells in this case. As I indicate in my last bullet there, to assign jurisdiction based only on one of the components could result in products with similar functions being in different jurisdictions, and I don't think that is going to be helpful; I don't think that is the right way for FDA to organize itself.

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Going back to the regulation of the structural endpoint, what is the issue? The cells? The current proposal would say that is a key issue. The scaffold? Cells in a scaffold are very, very different from cells alone. In fact, as I have already noted, it is very difficult to, in any way, discriminate between the function of the cells versus the function of the scaffold. You really must look at the integrated cells and the structure, not the individual components and design that lead to that integration.

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In the context of the proposed jurisdictional transfer, CDRH has historically reviewed a certain class of products, wound healing products being part of that. It seems to me, to transfer jurisdiction of such products at this time appears to be unwarranted. I really think it is premature. I think the dialogue needs to continue, but I think the issue is not simply moving from one part of FDA to another part of FDA. As I indicate

in my third bullet, transfer, in fact, may serve as an impediment to the further introduction of tissue-engineered products, particularly where you have platform technology, and I go back to my example one where the initial product, in fact, may fit well into CDRH but with the proposal the third generation, the further evolution of that platform technology takes it into biologics.

I don't in any way want to say that I think the current situation is ideal and that is does not need improvement. I think FDA needs to improve how it handles tissue-engineered products, but I think real improvement requires thinking out of the box.

So, the challenge then is how to define the regulatory pathway and process for these kinds of products. Someone asked me what I thought in terms of possibly moving things around in FDA and my comment was, it sounds to me like rearranging the decks on the Titanic. I really think a more creative process needs to be used and if, due to statutory limitations, the FDA structure cannot

accommodate this and does not serve the needs of the American public, then we need to be creative; we need to think out of the box and maybe congressional action will be required.

If congressional action is required, then I think FDA should work with the external community to make this happen. The bottom line is how we serve the American public not only in protecting them, but in making these emergent technologies available to patients. Thank you very much.

MR. BARNETT: Thank you. Let's go on to our next speaker, Ms. Carolyn Jones, from AdvaMed.

AdvaMed

MS. JONES: Good morning.

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I am Carolyn Jones, Associate Vice President of Technology and Regulatory Affairs department at AdvaMed. AdvaMed is the largest medical technology association in the world, representing more than 1000 innovators and manufacturers of medical devices. One of AdvaMed's principal roles is to support and facilitate laws

and policies that will bring --

MR. BARNETT: Excuse me, we are having some trouble hearing in the back, apparently. Maybe you should try it again.

MS. JONES: One of AdvaMed's principal roles is to support and facilitate laws and policies that will bring safe and effective innovative technologies to market expeditiously.

On behalf of our members, we come before this hearing today to express our strong opposition to any jurisdictional transfer of tissue-engineered wound products historically reviewed and regulated by the Center for Devices.

While the topic today is narrow, the jurisdiction of wound healing products containing live cells, we are concerned that any jurisdictional decision made in this area may also impact other extracellular wound healing and related structural repair products. We believe that the device status is critical to continued successful development of these products.

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We don't support the shift in jurisdiction for four primary reasons. First, there is no public health concern with the products being considered here today. Indeed, these products provide important public health benefits which should be supported by efficient pathways to market.

Second, premarket data uncertainties, if any, can be addressed through guidance and do not require sweeping jurisdictional change to accomplish that objective.

Third, CDRH regulatory initiatives have facilitated the development and marketing of these important products in their long pathway to market, and a change in jurisdiction would create new regulatory burdens, uncertainties and costs.

Finally, we believe there are legal, regulatory and practical impediments to a jurisdictional change.

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In considering the Federal Register's various inquiries, the agency's first question

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suggests that there are, or may be, public health concerns with this category of products and that these public health concerns might be addressed by some sort of jurisdictional change. AdvaMed is unaware of any public health issues presented by tissue-engineered wound products that have been reviewed or approved by CDRH. To the contrary, these products have had an excellent premarket and postmarket safety profile. Moreover, tissue-engineered wound healing products have been recognized as having extremely important public health benefits.

CDRH has recognized these many benefits. In CDRH's recent annual report, it cited wound healing products, such as Apligraf, Orcel and Dermagraft, as important advances in public health care and significant medical technology breakthroughs and, in recognition of their importance, has sought to facilitate their pathways to market.

There is no public health reason compelling a shift in jurisdiction for this

category of products, while the public health need for them is clear. We believe innovation will be fostered by continuing CDRH premarket review requirements.

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A strong theme raised in the agency's Federal Register notice is uncertainty regarding premarket review requirements for these products. The notice seems to suggest that premarket data uncertainties could be solved by a shift in jurisdiction.

AdvaMed believes that good guidances, not jurisdictional changes, are the most appropriate way to address any premarket data questions or confusion. CDRH historically has shown a willingness to issue guidances, with hundreds of guidances issued by the Office of Device Evaluation.

There are also other premarket reasons why CDRH should retain jurisdiction. For one, the center has extensive experience in the wound healing area. It has reviewed a wide variety of

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cellular and extracellular wound healing products over the years and its expertise has evolved with the technology. Additionally, CDRH has the specific clinical expertise important for the application of these products, for example, clinical expertise in the orthopedic, dental and related wound repair areas, areas that historically have not required extensive involvement by CBER.

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Finally, combination products do not prevent, and in fact encourage consultation as necessary to address any of the gaps in knowledge or experience. The statute and regulations both speak directly to the consultation process and, as you know, reforms are also underway to further improve this process. Therefore, to the extent that there are uncertainties or questions related to the type or scope of data that should be required for these products, AdvaMed believes these issues should be addressed through guidances or modification to existing guidances. Attempting to resolve any specific data issues by implementing a

sweeping jurisdictional shift will only create significant new regulatory burdens for industry. New regulatory burdens would slow the path to market far more significantly than any data uncertainties cited in the Federal Register notice.

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Other issues of importance to our members are the CDRH premarket review initiatives. Our members have taken advantage of a number of initiatives put in place by FDAMA as well as some of the CDRH reengineering activities: least burdensome, early collaboration, 100-day meetings, interactive PMA reviews, real-time labeling reviews, modular PMAs. Recently, several of our members have also been availing themselves of the humanitarian device mechanisms to allow earlier patient access to these technologies.

Ortec has made the dermal replacement product Orcel available to children with a rare skin disease, epidermolysis bullosa, for the treatment of hand deformities. We understand Advanced Tissue Sciences is pursuing a more general

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EB indication for its Dermagraft product, and Genzyme has pursued a HUD strategy for Epicel for use in certain patients with deep dermal or full-thickness burns. The HUD program exempts products intended to benefit persons with rare diseases or conditions from extensive clinical studies and, thus, makes these products available more quickly to those who need them. There is no comparable program to this in the Center for Biologics.

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These many device initiatives are the result of not just one but several statutory amendments, and legislative reform is expected to continue to respond to and foster innovation. By contrast, the statutory authority for biologics has evolved more slowly and infrequently over the years.

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CDRH's External Review Subcommittee, chaired by Dr. Robert Nerem who spoke prior to me, concluded that combination products need to be regulated with an approach that embodies the

philosophy of CDRH, one that is least burdensome, predictable, timely, flexible, transparent, interactive and effective. CDRH policy and practices have served the public well with respect to the wound healing products being discussed today, and AdvaMed strongly supports continued retention of device processes, authorities and personnel.

FDA's next questions in its Federal Register notice focus on the interpretation of primary mode of action and factors that should be considered in determining primary jurisdiction.

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These questions suggest that there already exists a definition or policy interpretation of primary mode of action that is based on the level of contribution of each component to the therapeutic effect of the product. Historically, the FDA has not interpreted primary mode of action in this way, and we understand this to be a relatively new concept that appears only to have surfaced in informal FDA discussions leading up to

this meeting. AdvaMed strongly opposes use of this new interpretation in determining primary mode of action for several reasons.

FDA's proposed interpretation appears to require the evaluation of the constituent parts of these products, which is largely unworkable for this class of products. The wound healing products under consideration are integrated products without clearly segregable components. These combination products are not like drug-eluting stents or laser-activated pharmaceuticals. Bear in mind here that all of the components of these wound procedures, that is, the synthetic and the extracellular, and the live cell components, work together to serve the same essential function of facilitating wound healing. It would be virtually impossible, and financially impractical, to tease out the level and type of contribution each synthetic and extracellular versus cellular components using current methodologies.

Instead, FDA and sponsoring companies quite properly have looked historically to the role

of the combined product, the integrated whole. They have concluded that, as a whole, the product serves as a replacement for the damaged skin in the wound bed. Like non-interactive wound dressings, they primarily provide a restoring environment for the wounds to heal although they are augmented with cellular components to facilitate the wound dressing's functionality. The functions of the combined product, thus, very clearly meet the historical definition of a device.

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There are also some legal impediments to the proposed interpretation of primary mode of action. From our initial legal review of these issues, there are at least four concerns that the agency will need to address.

The first is administrative law considerations. FDA regulations and policies have looked historically to the intended function of the combined product, not to the relative contribution of each component. Both the statutes and regulations at Part 3 refer to the primary mode of

action of the product and do not refer to its components.

Consistent with this authority, FDA's policy historically has considered the primary mode of action or function of the combined product rather than its constituent parts and, thus, the new language used in the Federal Register is at odds with various guidances that the agency has issued in this area.

For example, one important theme in the CDRH-CDER intercenter agreement is that combination products that have primarily a structural, physical or reconstruction purpose are regulated as devices. CBER also has historically supported this application of the definition of device in its proposed framework for regulation of cellular and tissue-based products. That document states that tissue-based products that are intended for diagnosis or therapeutic effect by physical action, including reconstruction or repair, and that contain synthetic or mechanical components and achieve their primary mode of action by means other

than metabolic or systemic action, are regulated as devices by CDRH. Likewise, in the CBER-CDRH intercenter agreement, it is expressly acknowledged that cultured skin will be regulated by CDRH under the medical device authorities.

We also have concerns regarding Part 3 considerations. We note that FDA's jurisdiction, regulations and philosophy provide that for products designated for review by a particular center, the agency may not change that center except for public health or other compelling reasons. While certain of the products being considered today may not have undergone a formal designation process, others have and, in any event, the same principle necessarily applies to all products affected by this hearing. Like companies that have received formal designations, all companies subject to this hearing have relied on the agency's interpretation to build their premarket development strategies, their markets and their business. Without a public health or other compelling reason, which we believe the agency has

not conveyed, jurisdiction of these products should remain with CDRH.

Statutory and definitional concerns-- AdvaMed also believes that the agency lawyers will need to grapple with statutory constraints presented by the definition of a biological product. Unlike a device or drug, which are fashioned primarily around intended use, the definition of a biological product is specifically defined by substances--viruses, therapeutic serums, toxins, antitoxins. This list of substances does not include structural cellular products in the mix and the legislative history of the Public Health Service Act, as well as case law, suggest that tissue and cellular products would be regulated separately, and not under the definition of a biological product. These definitional constraints will need to be dealt with in any contemplated jurisdictional change.

Finally, there are cost-benefit factors that we have all long recognized under Executive Order 12866--that it should evaluate and weigh all

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costs and benefits of alternative regulatory environments. I am running out of time here so I am going to skip to the last slide.

[Slide]

Combination products containing live cellular components have been regulated for a decade by CDRH. It is inefficient to change jurisdiction. It will increase the burden for manufacturers, slow development of tissue-engineered wound healing products, and we don't see that the change is justified by any public health concerns.

MR. BARNETT: Thank you, Ms. Jones. Dr. Zoon?

DR. ZOON: Yes, just a clarification, I just wanted to let the meeting participants know that CBER is one of the few centers that actually uses multiple regulatory schemes. We have our biologics regulations scheme which includes INDs and BLAs. We also have device regulations under 510(k)s and PMAs, and have products that currently fit this category. In addition, we also use, as

appropriate for a certain small class of products, NDAs. So, I just wanted to clarify the regulatory framework for the Center for Biologics, especially cost cuts, the device area, the traditional biologics area, as well as appropriate certain classes of NDAs. Thank you.

MR. BARNETT: Anyone else? No? Thank you, Ms. Jones. Our next speaker is Mr. David Smith, from the Tissue Engineering Society International and the Pittsburgh Tissue Engineering Initiative.

**Tissue Engineering Society International and
Pittsburgh Tissue Engineering Initiative**

MR. SMITH: Good morning.

[Slide]

My name is David Smith. I am here on behalf of Tissue Informatics, where I am senior vice president and general counsel. Obviously, this is not the first time that the FDA has had an opportunity to consider how best to classify a medical product containing human cellular materials.

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The first such hearing was back in 1995, in November of 1995. In fact, some of the entities that I am here to represent today, the Pittsburgh Tissue Engineering Initiative, the Tissue Engineering Society International and, for that matter, even my own company, Tissue Informatics effectively did not exist at the time of that hearing, which is an indication of how much has been accomplished in the field of tissue engineering between November of 1995 and June of 2002.

The Pittsburgh Tissue Engineering Initiative was created to bring together researchers from multiple institutions within the Pittsburgh area, from multiple disciplines and multiple backgrounds to begin to develop tomorrow's tissue-engineered medical products.

The Tissue Engineering Society International, likewise, is an opportunity to bring together scientists and researchers from around the world, again, looking towards the development of

tomorrow's engineered medical products.

Tissue Informatics is not a tissue-engineering company but we hope to be able to support that industry as it grows.

I mention ASTM on this slide because I think it is another important part to mention in conjunction with looking back from 1995 to the present, and realize how much has been done by the FDA to reach out to the larger community and understand some of the safety and efficacy issues associated with this emerging technology, and to note in particular the efforts of the Center for Devices in launching the effort by the American Society for Testing and Materials to develop a specific section dealing with standards for engineered tissue medical products.

[Slide]

Dr. Nerem has already gone through some of these points, and it is important to note that, clearly, the industry has grown considerably from its early roots but it still has a long way to go. There are a number of companies, most of which are

still private companies and still very much in the start-up phase. There are 1.6 publicly traded companies, with approximately almost two and a half billion net capital value. I mention today, and I also reiterate the point that Dr. Nerem mentioned about the color red, if you look at what has happened to those companies, and what may be anticipated for those companies going forward, it is not necessarily the rosiest of pictures.

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As of the end of 2000, the market capitalization for just the publicly traded tissue-engineering companies in the United States was approximately two and a half billion dollars. That market capitalization has shrunk to almost a billion dollars in approximately 12 months. Over the entire lifetime of just these publicly traded companies, there is an accumulated deficit of over two and a half billion dollars, which has only been incrementally offset by the amounts that have been earned by these companies through product revenues with the few products that are presently lawfully

marketed in the United States.

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If you think about that, one of the major challenges for the existing companies, but particularly for the companies still to come into being, is this challenge of recovering the research and development costs. Established products may expect that after the research and development phase, through the manufacturing and marketing phase, the initial effort and expenditures to develop that product will be recovered through product sales. It is not really clear when that time comes for engineered tissues. Hopefully, it will come but presently we are not able to say that any particular company has, in fact, achieved that.

The significance of that is that so much of this research that has occurred to this point to bring the products to market that are presently on the market has been accomplished through private financing. In the absence of a belief in the private markets that there will, in fact, be that day when that line will cross the center point and

begin to move into positive territory, it will be extremely difficult, certainly, to sustain the companies that are presently in business but, more importantly, to bring into being the companies that are looking to develop perhaps the more significant engineered tissue products that maybe are in the minds or simply on the laboratory benches of the scientists and researchers that form the parts of the Pittsburgh Tissue Engineering Initiative and Tissue Engineering Society.

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So, the public and private financial support for this idea of product development is the balancing of value and risk. In an economic sense, that is a return on investment. In a societal sense, it is clearly improvement in health. The risk is the cost of market acceptance. There are, obviously, many costs of that, not the least of which is regulatory approval but certainly not necessarily the most significant, and there are positive aspects to a careful scrutiny of emerging medical products to assure that the societal risk,

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the improvement in health, is realized in addition to the return on investment.

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It was my privilege to be a part of the study on tissue engineering research that evaluated the state of tissue engineering research in Europe and Japan and to compare that to where the United States stood as of 2000. This was a study that was supported by the agencies that are listed on this slide. Although, clearly, the bulk of the study was directed to assessing where the United States stood in relation to a number of scientific concerns, one of the areas that was assayed during this study were legal and regulatory issues. One of the things that rang clearly through that study was that the lack of clear regulatory approval pathways across all major markets increases the cost and time to market worldwide.

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The challenge of this regulatory uncertainty can be seen in two forms. Particularly in Europe, the challenge is the fact that there is

no clear path, that established approval paradigms have not yet been tasked for products incorporating living tissues. In the United States, perhaps this hearing suggests that there is another facet to that problem, which is an unpredictable path. The approval paradigms that have been established for products incorporating living human tissues are not predictably applied.

This is in essence a classification problem and, obviously, the clear challenge is applying existing, perhaps in the context of engineered tissues, archaic statutory definitions to a new medical technology. Without belaboring these particular definitions, I would suggest that it is not necessarily clear that either of these definitions specifically includes or specifically excludes an engineered tissue product.

[Slide]

Clearly, in fact, the FDA I think has recognized that itself in some of its earlier pronouncements in this area. The May, 1996 guidance on applications of product comprised of

living autologous cells notes the possibility that these products could be classified as biologics or as device products because of some of the similar features that they may share.

Again, in the proposed approach to regulation of cellular and tissue-based products, there is certainly no clear statement that certain kinds of products, by definition, cannot be considered to be one particular type of product or another for purposes of regulatory classification.

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The challenge of uncertain classification is to place developers of new medical products in this field in the untenable, I would say, position of having to walk a very fine line between two regulatory centers, uncertain of which way the balance will ultimately tip. As Dr. Nerem pointed out, there is the possibility that that balance may actually shift in the process of marketing the particular product that has already been approved and classified as one particular type and now that classification is shifted.

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To meet this challenge of uncertain statutory classification, on behalf of the products still to come into being, I would urge you that no immediate reclassification of approved medical products occur in the absence of a clear, compelling safety emergency. Such an immediate reclassification of products, I would suggest, suggests to those people who, in the process of sustaining this industry through their financial support for emerging companies and who might be persuaded to continue that support into the future, will look at that kind of a change and question whether or not, indeed, there ever will be that return on investment, both in terms of improvement in health as well as its economic return.

In the event that there should ultimately be a reclassification of approved products, that should not take place in the absence of a clear, detailed classification rationale providing a predictable entry point so persons developing a product will know, before they have come to the

FDA, the likelihood that a product will be classified as one thing or another, and clear, predictable divergence points if, in fact, it is necessary that there should be a shift over time, not that I would encourage that.

Nevertheless, the absence of that predictability, in the absence of being able to anticipate, first of all, how you will be classified and, second of all, whether or not the classification may shift over time, greatly complicates the process of developing a product. I would suggest that perhaps the best approach is to moderate these classifications by true intercenter collaboration.

[Slide]

What I mean by that is a collaboration that really transcends the assumption that a medical product is a combination of divisible parts, susceptible to serial regulation. I would urge you to take a look at kind of the foundation of the science itself that brings these products to the agency in the first place. It is really the

multi-disciplinary aspect of tissue engineering that makes it possible to create these products in the first place.

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What I mean by that is that if you look at centers that have emerged to create these new technologies, if you look at Dr. Nerem's center in Atlanta, if you look at what is occurring in Pittsburgh and other places around the United States, our abilities to develop these new technologies are based upon the establishment of really seamless interactions between experts in critical fields in science. Really, it is that blending of disciplines, not maintaining necessarily finite distinctions between them but making sure that each has the benefit of the best of all of them, that really leads to that amalgamation.

If you look at the picture on the right, you might be able to pull out a particular color but you wouldn't necessarily be able to describe the painting by that one color. It really depends

upon the integration of all of those colors to create the unitary whole.

One thing I would add along those lines is that if you think of other things that have occurred since 1995, perhaps one of the most striking things has been the dynamic reengineering efforts that have taken place both through the agency's own initiation and perhaps also, to some degree, through congressional initiation and through the Modernization Act.

I had the privilege of participating in the Center for Devices reengineering effort to reestablish the product development protocol, and I was really struck by the great opportunity for flexibility with the right approach, recognizing that the right challenge is to find the proper balance between these shared risks between product sponsors and the agency, and a look to creating this kind of a seamless interaction of all the regulatory paradigms, recognizing the complexity of these particular medical technologies. Thank you very much.

MR. BARNETT: Thank you. We have a break scheduled for ten minutes at this point. We can make that 15 minutes. I have 10:10 so let's make it 10:25.

[Brief recess]

MR. BARNETT: Our next speaker is Ms. Sara Radcliffe, of PhRMA. Ms. Radcliffe?

PhRMA

MS. RADCLIFFE: Good morning, and thanks very much for the opportunity to speak to you this morning about combination products containing live cellular components.

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I have structured my presentation to answer the questions asked by the agency in turn. With respect to the public health concerns, PhRMA agrees that there is potential for public health concerns that need to be addressed in a consistent manner within the agency.

The primary concern is the potential transmission of infectious agents, resulting from such issues as tissue sourcing and cross-

contamination from improper or uncontrolled processing.

With respect to manufacturing, the manufacturing of cell therapy products needs to be in strict accordance with good manufacturing practices, including controls over sourcing of materials, process validation, environment controls, containment during processing, patient identification and tracking by lot, and product release testing. This would apply to both biological and biomaterial components and the melding of these into a final product.

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With respect to the data needed to demonstrate safety and efficacy, we believe that safety and efficacy of these products should be demonstrated in controlled clinical trials, ideally randomized, blinded, placebo-controlled. However, we recognize that controls may not always be possible or appropriate and, therefore, flexibility is necessary and should be appropriate to the clinical application. Factors to be considered

should be whether you are dealing with met or unmet medical needs; fatal versus non-fatal conditions; and other issues.

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CDRH or CBER? Both are charged with protecting the public health. Is there a greater public health risk with cell-based wound healing products being regulated in CDRH? We do not think so.

Is there a greater history and expertise in regulating synthetic and biomaterials in CDRH? We think clearly there is.

Is there a greater history and expertise in regulating biological systems and their products in CBER? Clearly, yes. Will cell-based products in combinations become more complex? Certainly.

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We think that any scaffold, matrix or biomaterial supporting cells should be considered as a delivery system for optimizing or facilitating the effect of cells being delivered. The device matrix is a cell delivery system, while the cells

provide a dynamic environment promoting healing. The matrix optimizes the effect of those cells. Therefore, the combination is a drug delivery system, a bioreactor in situ, delivered in a complex array of growth promoting factors.

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Just to go over the evolution of biological product regulations which are probably well-known to most here, in the past biological products were historically complex, difficult to identify, characterize and quantitate, and they were often defined primarily by activity in a bioassay. Therefore, both the product and the process were licensed, and that ensured that even if the product could not be fully defined it would be manufactured the same way each time. All changes to the license process required CBER approval prior to implementation. As analytical procedures have become more precise, there have been changes in the regulations, especially for specified products and I have listed some there.

[Slide]

The definition of a device--any instrument, apparatus, implant intended to affect a structure or any function of the body which--and here is the significant part--does not achieve its primary intended purpose through chemical action within or on the body, and which is not dependent upon being metabolized for the achievement of its primary purposes.

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Definition of a biologic--a biological product means any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product or analogous product.

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With respect to what information the agency should use to determine which mode of action is primary, based on the definitions I just went through, it seems that the important question is whether the efficacy is dependent on chemical action or upon being metabolized or not. In the clinical scenario with these products, typically

you would be evaluating the matrix, the wound covering or barrier alone versus the matrix with the cells.

We think that when jurisdiction is not obvious over these products the decision should be made within the Office of the Commissioner with the assistance of intercenter expert panels and advisory committees.

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So, here are our recommendations. We believe that cell-based wound healing products currently approved through CDRH should remain within CDRH. That would ensure consistent review treatment as originally approved. However, for new indications when non-wound healing applications of these products are proposed, we think that review should be based on mode of action, not historical approval mechanisms or claims or lack of claims so that parity of regulations can exist.

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Products containing living cells should be regulated within CBER's Office of Cell and Gene

Therapy, and that would be for cells alone used for structure or function and for cells in a biomaterial or synthetic matrix. Matrix components supporting cell delivery or function should be reviewed within CDRH as a consult to CBER.

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In order to ensure consistency of regulation and review, again, jurisdictional issues should be handled through the Office of the Commissioner with representation from the relevant centers, and there should be standardized and routinely updated intercenter agreements focusing on primary mode of action as the criterion.

PhRMA proposes that a draft guidance be published within six months of the close of the docket outlining classification of and jurisdiction for such products; processes for communication for CBER and CDRH; performance targets; and a time line for publication of revised intercenter agreements, preferably no more than 18 months from now. Finally guidance should be issued within 12 months from publication of the draft guidance.

With respect to process, we believe that there should be equal accountability between the lead and consult centers, and that the time line should be clear. They should proceed on the basis of the lead center such that manufacturers understand ahead of time what those deadlines will be. Thank you very much.

MR. BARNETT: Thank you. If there are no questions for the panel, our next speaker is Dr. Gary Gentzlkow, from Advanced Tissue Sciences.

Advanced Tissue Sciences, Inv.

DR. WARREN: My name is Ron Warren. I am executive director of regulatory affairs at Advanced Tissue Sciences, a company committed to redefining, developing and marketing tissue repair products.

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On behalf of ATS and Smith & Nephew, our marketing partner, we are here to explain why our companies strongly oppose any jurisdictional transfer of our tissue-engineered wound products which historically have been reviewed and regulated

by the Center for Devices.

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For more than a decade we have invested millions of dollars into the premarket development and marketing of tissue-engineered products as medical devices. Our first generation of efforts has been devoted to wound healing applications and, from these long and hard efforts, ATS now has approval to market Dermagraft, a dermal substitute for the treatment of diabetic foot ulcers, and TransCyte, a human-based temporary skin substitute for the treatment of burns.

We also have clinical investigations of Dermagraft in periodontal wounds, venous and pressure ulcers and, most recently, we have sought and obtained a humanitarian use device exemption for treating epidermolysis bullosa.

As a final aspect of our first generation wound healing products, we are developing tissue-based products for the repair of damage to articular cartilage defects.

As you can appreciate from this platform,

the issues before this hearing today are of critical interest to my company.

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We will be providing two perspectives today on why transfer of our devices to CBER is neither justified nor warranted. Dr. Gentzlkow will first provide a premarket review and public health perspective and I will then close the discussion by offering our views as to why it is critical that our existing device status obligations and rights are preserved.

As you will hear from us this morning, without assurances that device status will continue, we believe there is a risk, not only for this company but for the entire industry, that much of this important technology will simply be left on the research bench and not reach the marketplace.

I would like to introduce Dr. Gentzlkow to speak now.

DR. GENTZLKOW: Thank you, Ron and distinguished panel and audience. I appreciate this opportunity to convey ATS' concerns about this

important issue.

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Before addressing the specific issues in the Federal Register, there are some general things that we want the agency to consider. First, I would like to address the public health issue. The Federal Register inquires about, quote, the public health concerns related to these combination products as a whole and with respect to their components.

This is the first in a long series of questions and we are concerned that giving this prominence in this way might leave an erroneous impression that there actually are public health concerns with this category of products. I don't know if that was the intended impression but, if it was, we respectfully disagree.

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I offer three observations on the general safety profile of our products. First, all safety-related issues with ATS' products have been thoroughly addressed through the device premarket

review and labeling processes. Dermagraft and TransCyte, the two ATS products approved so far, were first put into clinical studies in 1991. Yes, at that time when such products represented entirely new technologies and theoretical concerns about safety were raised. Eleven years later, the agency has had more than a decade to consider these products and any theoretical safety concerns have long since been addressed.

Second, since approval several thousand patients have been implanted with either Dermagraft or TransCyte. During this time they have demonstrated a remarkable safety record. As it was during the premarket clinical experience, there have been no safety problems that could be regarded as caused by either product.

As a third observation, not only did these products represent no public health concerns, to the contrary, they have been recognized as having extremely important public health benefits by the medical community, by the patients who benefit from them, and by the agency itself.

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For example, foot ulceration is the most common complication of diabetes that requires hospitalization. In addition to causing patients significant morbidity, it can lead to amputations and other forms of serious disability. Dermagraft addresses this disease.

TransCyte has an equally compelling public health benefit. Just as one example, in the days following 9/11 FEMA assisted our company to provide an urgent special shipment of TransCyte, which was used to care for burn victims from the Pentagon.

With products that provide such an important and often life-saving benefit, the pathway to market should be impaired.

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As a secondary introductory theme, the Federal Register notes that the successful development and marketing of these products may be slowed by uncertainty about premarket regulatory requirements. We applaud the agency's desire to avoid premarket regulatory problems that might slow

the path to market. However, if there are any uncertainties as to premarket requirements we agree with the position that Advamed put forth this morning, namely, that guidance is a solution to those issues.

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Shifting jurisdiction will not solve the narrow data uncertainty issue and, instead, will create many new uncertainties, burdens and costs which, in turn, will slow the path to market, something the agency is expressly wishing to avoid.

On the Federal Register's more specific premarket data questions, we believe that Dermagraft provides a good example of how CDRH has applied reasonable data requirements tested by time. Over the last several years, the three FDA centers together have prepared a draft guidance document on chronic cutaneous ulcer and burn wounds which, by the terms of the document, each center will implement. Thus, it is unclear why question one asks about information the agency should require in premarket submissions. FDA multi-center

guidance on that question already exists.

This draft guidance was a work in progress during the Dermagraft PMA review. CDRH essentially followed this draft guidance with respect to preclinical and clinical data requirements. The review process was properly tailored to address relevant safety and effectiveness issues. There is not time now to list all the testing that was done, but if there are questions I have slides that list those studies.

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Our experience is that premarket requirements, submissions and expertise have evolved very nicely within CDRH. I personally have worked with CDRH reviewers over the entire ten-year period. Yes, there were problems in the early years as the knowledge base had to be acquired, but CDRH has done its homework, obtained consultation when appropriate, and developed expertise over a long period of time. We, therefore, urge the agency not to fix that which is not broken or, worse, not to break that which is working fine.

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Just as it is instructive to consider those issues that should be reviewed at the premarket stage, it is also useful to consider what premarket issues are inappropriate or excessive for products of this type. Drugs and biologics, because they often act systemically, often require a different kind of surveillance for safety, requiring much larger populations to be studied premarket in order to uncover potential adverse consequences that can arise in any body, organ or system.

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A good example is CBER's review of the OMJ Pharmaceuticals' BLA for Regranex, which is recombinant protein product that, like Dermagraft, is intended for diabetic foot ulcers. Because of the nature of recombinant protein products and their systemic issues, there were 81 pharmacology tests; a battery of pharmacokinetic tests that included studies in primates; a pivotal clinical study program that included 925 subjects for

efficacy and nearly 1800 subjects for safety review. I think it is fair to say that had Dermagraft been forced to follow such a preclinical and clinical pivotal pathway, a model ill-designed for a human tissue product, it would be at the premarket stage still or, indeed, may not even have been pursued given the size and resource limitations of our company.

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Also, Biologics' concepts such as identity, purity, potency and the like are often not applicable to tissues, nor should one expect that they would be since the biologics statutory framework was built around blood and blood products, viruses, therapeutic serum, toxins, antitoxins and allergenic products, all of which are quite different by their very nature.

Let me pause here to note that our support for CDRH is not intended in any way to criticize CBER, and we have the greatest respect for the extremely able scientists in CBER. Nor are our comments intended to suggest that the CDRH pathway

to market is without regulatory hurdles or difficulties. ATS' products were in development for a decade and the premarket data requirements were extensive.

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However, the point we are trying to make is that CDRH's law and premarket approaches are fundamentally more amenable to flexible review and to fostering innovation than are the law and approaches followed by CBER.

You have already heard from AdvaMed about a number of device premarket initiatives. These premarket initiatives have been important in advancing this unique and innovative technology. For all of these premarket reasons we strongly believe that CDRH continues to be the appropriate center of authority. There is simply no problem that the agency needs to fix. Thank you very much. I will turn it back to Ron Warren.

MR. WARREN: Thank you.

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In responding to the next series of

Federal Register questions, my comments will focus on three topics in particular. First, the concept of primary mode of action; other factors that should determine jurisdiction; and, finally, the consequences and concerns of shifting jurisdiction from Devices to Biologics for this category of products.

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Beginning first with the agency's questions concerning the primary mode of action standard, as AdvaMed, we strongly support the agency's historical interpretation of this concept and believe that any informal new interpretation, such as level of contribution of each component, is inappropriate from both a regulatory and science perspective. Any new interpretation, particularly one that serves to shift jurisdiction, would represent a substantial departure significantly affecting this industry.

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In the case of Dermagraft, there are several reasons why the product's primary mode of

action has been and should continue to be considered a device. First, when you view the product as a whole, which regulation, policy and historical precedents tell us to do, the product serves as a human dermal replacement for damaged skin in the wound bed. The fibroblasts, which co-exist with the structural mesh and extracellular matrix, are mature and do not undergo further alteration or organization post-implantation. The product, once implanted, persists for some time in the wound bed. The product, thus, has all the attributes of a human dermal substitute, and frank substitutes or replacements have been reviewed consistently as devices over the years.

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The desire of the agency to parse out the relative contributions of Dermagraft components is at odds with what is known about this product. The product's synthetic, extracellular and cellular constituents are not clearly divisible, and all work together to achieve wound healing. Any testing on component contributions, in our view,

would be costly, would serve no clear public health purpose and, in fact, may be impossible to undertake given today's technology.

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The Dermagraft product is, at its essence, a wound dressing. It provides an environment that facilitates wound repair. The three-dimensional scaffold and extracellular matrix are analogous to a large number of non-interactive wound dressings currently under 510(k) review, and the mature fibroblasts imply augment the essential wound dressing function.

For example, Cook's Oasis non-interactive wound dressing product, which contains collagen and other macromolecules but not live cells, has been described in press releases as providing a natural scaffold like a cellular matrix with a three-dimensional structure and biochemical composition that attracts whole cells and supports tissue remodeling. This example highlights the seemingly arbitrary delineation that the agency is attempting to make between live cell and other wound products.

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Rather than drawing arbitrary distinctions between those wound products that have live cells and those that do not, a distinction that we do not believe can be sustained because of the principle that like products must be treated comparably, we urge the agency to maintain its historical interpretation.

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Next in your series of questions, you have asked what factors should be considered in the assignment of jurisdiction, and what the hierarchy of those factors should be.

Our legal advisors tell us the foremost among factors would be those of law, and AdvaMed has provided industry's preliminary views on those issues. Besides law, there are several other factors that weigh in and support existing device jurisdictional decisions.

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You have heard already from Dr. Gentzlkow about the many premarket reasons supporting device status. I can add one further comment, and that is

that the greater flexibility of the device premarket review structure is more in keeping with the risk-based philosophy initially envisioned by the agency for cellular and tissue-derived products. Bear in mind in this regard that cadaveric tissue and bone products, also used for wound healing and structural purposes, also local in nature, and with comparable efficacy issues and arguably greater safety concerns undergo no premarket review.

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There are also manufacturing considerations supporting device status. Our manufacturing facility is registered as a medical device establishment by the FDA, as a manufacturer and/or tissue bank by relevant states and, in January, 2003, as a tissue processor under FDA regulations.

Our marketing experience has demonstrated that device quality systems ensure postmarket safety, and the flexibility of the device quality systems best accommodates these products.

Buttressing these device requirements, as I said, is the full panoply of existing and proposed federal and state tissue processing regulations which address tissue-specific quality issues, not squarely addressed by device QSR requirements.

We, thus, already have a comprehensive and complicated series of manufacturing requirements, and any proposed imposition of biologics regulations to this existing matrix would be costly, confusing and unnecessary.

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There are also compelling equitable reasons to support continuing device jurisdiction. The company's long-standing regulation by CDRH has led to a well-entrenched device orientation. All of our systems, our people, our development strategies, our compliance programs, and our marketing apparatus, in short our entire business, has been as a device company. To now attempt to call us a biological-regulated company would require us to invest substantial funds in the implementation of new regulatory systems, new

personnel and new short- and long-term product development plans.

We ask, as a matter of equity, that the agency consider very carefully this potential substantial harm not only to ATS, but to other companies similarly situated. As part of this process, we also would ask that the agency consider very carefully whether any perceived administrative benefits from this proposed jurisdictional change could ever outweigh such significant costs.

As a closing thought, I would like to reflect on this issue, not only as a company representative but as a regulatory professional--a position I view as a bridge between product innovators and patients in critical need. The process presents complex regulatory requirements and lengthy time lines, but I am encouraged by the clinical results we are seeing. We continue to hear how our products have made a difference, helping to treat a burned child who had pulled a pot of boiling water onto himself, or a patient with diabetes whose open sore on the bottom of her

foot has healed after years of treatment with more traditional methods.

From this perspective, we, at ATS and Smith & Nephew, urge FDA to continue to support that which CDRH has sought to do, to take a least burdensome approach to foster safe and effectiveness tissue-engineered products which hold the promise of redefining the way we treat injury and disease. Thank you very much for your time today.

MR. BARNETT: Thank you, Mr. Warren. Two comments?

MS. COOK: This is really a request. Both you and Ms. Jones, from AdvaMed, mentioned a historical interpretation of primary mode of action. I think we would be interested in seeing submissions to the docket on what you believe this historical interpretation to be.

MR. WARREN: We would be happy to do that.

MR. BARNETT: Dr. Zoon?

DR. ZOON: Thank you for your remarks. Since the presenter talked about tissues, I just

felt it was appropriate for the audience to understand that part of the tissue framework that we are currently developing under the agency's initiative deals with a matrix of risk-based regulation that actually spans bank to human tissue through cellular gene therapy and xenotransplantation. Much of the oversight of that program is going to lie under the purview of the Center for Biologics and, certainly, working with the Center for Devices as appropriate.

But I think it is important for folks to know that we will be using different approaches based on the risk factors and a risk-based approach to the regulation of tissue and cellular-based products that go from no premarket applications with primarily registration and listing and oversight through inspectional approaches, through a higher degree of regulation of these products depending on the risk factors.

I just wanted to clarify that in the context of the whole because I do think there is a perception when people talk about the Center of

Biologics to only think about BLA and IND regulated products, and I think it is important to look at the spectrum. Thank you.

MR. BARNETT: Thank you. Anyone else on the panel? If not, thank you, Mr. Warren. Our next speaker is Dr. Michael McGuire, University of Texas.

University of Texas

DR. MCGUIRE: Good morning.

[Slide]

My name is Michael McGuire. I am a periodontist in full-time in private practice in periodontics in Houston, Texas. I am also associate professor of periodontics at the University of Texas Health Science Center in San Antonio and in Houston, and I am currently the immediate past president of the American Academy of Periodontology. I am consultant on evidence-based dentistry to the Council on Scientific Affairs of the American Dental Association, and I serve on the editorial board of several journals on periodontics and dental implants. In addition to that, I have

been the principal investigator in numerous practice-based clinical trials on new dental technology, and have published broadly in peer-reviewed journals in this field, and have received the Clinical Research Reward from the American Academy of Periodontology. I am also a physician sponsor of a device investigation to evaluate the safety and efficacy of a commercially improved product as a substitute for autologous grafts. As a result of all this, I feel I am qualified to speak to you about the issues before the hearing today.

I requested the opportunity to speak so that I might share with you my experiences with tissue-engineered devices in the periodontal arena, and my views on the need for this important technology to reach the market in as expeditious and as least burdensome means as possible.

[Slide]

Assuring that there is adequate hard and soft tissue around teeth is critical to periodontal health. Periodontal disease is a widespread

problem in the United States and the Surgeon General has reported that the percentage of adults with severe periodontal disease is significant and increases with age so that we can expect it to be an increasing public health problem as the baby-boomers age.

According to the American Dental Association, approximately 400,000 people undergo periodontal soft tissue surgery annually in the United States. These statistics highlight the importance of ensuring that there is adequate treatment in place to address this significant health problem.

[Slide]

In order to cover exposed roots and repair damaged gums we usually harvest tissue from the roof of the patient's mouth and graft it into the deficient area. Autogenous grafts require a second surgical site to harvest this donor tissue, which causes increased discomfort and risk to our patients. To confound the problem, because of anatomical and structural limitations, patients

often do not have adequate supplies of autogenous tissue to cover multiple teeth with extensive soft tissue loss. As a result, grafting procedures often require multiple surgeries. Because of the limitations associated with this technique, we are looking for a viable alternative that will provide unlimited supplies of off-the-shelf tissue for periodontal soft tissue repair, thus, reducing the pain and discomfort of patients and limiting the number of surgeries that the patient has to undergo.

[Slide]

Tissue-engineered products containing live human cells that are seeded on a synthetic matrix show great promise for fulfilling this need. Most importantly, because they provide unlimited supplies of viable tissue, they reduce the need for additional surgeries and multiple surgical sites. Larger areas can be treated in a single surgery without requiring any donor tissue, thus, reducing the additional discomfort and risk to our patients.

[Slide]

I recently conducted a 20-patient pilot study in periodontal patients to assess the safety and efficacy of Dermagraft in establishing a functional zone of attached gingiva. The preliminary results of this study demonstrated that Dermagraft did, indeed, generate new attached gingiva. Because of the promise of this technology and the fact that it reduces the risk for my patients while offering all of the benefits associated with autogenous grafts, there should be no regulatory burdens that unduly impede its availability.

[Slide]

Tissue-engineered products in the periodontal arena, including those with cellular components, serve the function of providing a matrix for regeneration and repair. Dermagraft performed effectively in my study as a substitute for autogenous palatal connective tissue grafts. We biopsied some of the sites treated, and the histology revealed normal-looking connective tissue, covered by keratinized epithelium on both

test and control teeth. A blinded examiner was not able to distinguish which biopsy was generated using Dermagraft versus the palatal donor tissue.

[Slide]

I understand that structural tissue-derived periodontal products and other products that make biological claims about regeneration and repair historically have been regulated by the Center for Devices. I further understand that a vast array of dental products, including products for periodontal grafting, augmentation, reconstruction, membranes for tissue regeneration and aids to wound healing have results from these review processes. The necessary periodontal and dental expertise resides in this center, and the periodontist and the dentist in the dental review branch have evaluated tissue regeneration and other products for many years, and are familiar with the product design and performance characteristics most important for periodontal products. In my dealings as an investigator with this branch of the FDA, I have always personally found them to be very

knowledgeable about the nuances of periodontal clinical trial design.

[Slide]

In addition to that, as an officer of the American Academy of Periodontology, I have also been involved in initiatives that have spanned over a ten-year period involved in sharing knowledge and educating the dental device branch about clinical trial design for periodontics and what constitutes a clinically significant outcome.

As a result, I consider the Dental Device Branch to be the center of expertise in the FDA in this area. I believe the dental experience and background found in the dental device group is optimal for review of structural products for periodontal grafting, like ATS' product Dermagraft.

The mouth is a unique environment, with special concerns of high bacterial load, the mechanical challenges that need to be addressed by a group that has experience with clinical trial design and outcome assessment in this field.

[Slide]

In conclusion, there is a great need for viable alternatives for the autologous donor tissue for periodontal grafting. As our population continues to age and periodontal disease becomes more widespread, there will be an increasing need for alternatives to the autogenous graft. As a periodontist, I am very excited about the prospect of having tissue-engineered periodontal devices available to treat my patients and see them as offering immediate benefits while reducing the risk to my patients.

It is my hope that the jurisdictional discussion today will not result in any additional regulatory obstacles that could slow or impede the continued development and patient access to these important products. Thank you for the opportunity to speak today.

MR. BARNETT: Thank you, Dr. McGuire. If there are no questions from the panel, I will call on the next speaker, Ms. Judith O'Grady of Integra LifeSciences Corporation.

Integra LifeSciences Corporation

MS. O'GRADY: Good morning.

[Slide]

I am Judith O'Grady, Vice President of Regulatory Quality and Clinical Affairs for Integra LifeSciences Corporation. I would like to thank FDA for the opportunity to speak at this open public session regarding combination products containing live cellular products.

Integra's skin replacement system is a first in these series of products that has been reviewed and approved by the Food and Drug Administration, the Center for Devices and Radiological Health.

[Slide]

The objectives of my talk today will be to review what Integra is as a skin replacement system, review the current regulatory requirements for product approval of skin replacement products under the Center for Devices, recommendations for data to support safety and effectiveness, and recommendations for FDA jurisdictional products intended for wounds and products that contain live

cellular products.

[Slide]

What is Integra? Integra is a dermal replacement system. It is a skin replacement system. It is indicated for the post-excisional treatment of life-threatening full thickness or partial thickness dermal injuries when sufficient autograft is not available or desirable due to the condition of the patient.

Also, a recent new indication is repair of star contractions when other therapies have failed or when donor sites for repair are not sufficient or desirable due to the physiological condition of the patient.

[Slide]

Integra is an innovative technology in the wound healing area. CDRH annual reports have listed Integra as a significant medical technology breakthrough, considered an important technology to be available after the September 11 terrorist attacks; approved in 1996 and regulated as a Class 3 medical device under the premarket approval

processes under CDRH; regulated as a medical device for over 20 years. So, when I review this, indeed, the Center for Devices has been extremely rigorous in review of this since the first IDE in 1982. It is regulated as medical device in the European Union, Canada, Japan, Australia and other countries where the product is currently registered, for a total of over 30 countries. Most importantly, Integra, though a skin replacement system and has a claim for regeneration of dermal tissue, does not contain any live cellular components or recombinant proteins.

[Slide]

A description--it is a bilayer membrane skin replacement system for full-thickness injuries. It is a dermal replacement layer and temporary substitute layer. The dermal layer, again, has no live cellular components. It is a three-dimensional matrix of cross-linked bovine collagen and glycosaminoglycan conjoint 6-sulfate. It has a controlled porosity, defined degradation rate and promotes cellular ingrowth.

[Slide]

The temporary epidermal layer is a silicone layer. It controls moisture loss from the wound and protects the wound.

[Slide]

The dermal replacement layer serves as a matrix for the infiltration of fibroblasts and capillaries. The endogenous collagen matrix is deposited by fibroblasts while the dermal layer is degraded. Upon vascularization of the neodermis, the silicone layer is removed and the thin meshed epidermal autograft is placed over, and cells from the epidermal autograft grow and form a confluent epidermis with stratum corneum.

[Slide]

It serves as a template to generate new dermal tissue, neodermis. It provides immediate physiological wound closure and its functional dermal tissue.

[Slide]

One of the most important parts of this review by CDRH was histology. There are over 336

serial biopsies from 130 patients treated with Integra, and intact dermis was achieved with regrowth of apparently normal reticulum capillary dermis. Critical for this product as well as for the others we are talking about today, these are life-saving and also improve the quality of life, with no scar formation appearing at any time during the course of healing and the biopsies of the patients observed.

[Slide]

I just want to briefly go through some of the studies required under this rigorous review by CDRH for the initial approval of this product: extensive safety and effectiveness data; biocompatibility data, conducted according to ISO 10933, including the following studies, immunogenicity studies, both preclinically and clinically during the clinical trial; preclinical wound healing studies; multi-center controlled, randomized clinicals. Two additional trials were submitted in support of the PMA. Additionally, which we will go into, some of the rigorous post-

approval study requirements of this PMA, a post-approval study was done in 216 patients, 841 wound sites. For the initial indication there were over 444 patients, over 1000 wound sites were evaluated.

[Slide]

Baseline evaluations, wound site photographs, biopsies, culture and lab testing. Each patient served as their own control. Acute and long-term follow-up was required in support of this PMA, up to a year, with, again, laboratory testing and wound site evaluation and biopsies; patient evaluations, investigator evaluations, immunological evaluations and histology of the wound sites.

[Slide]

Conditions of approval--a post-approval study. I will be talking about the type of studies that can be recommended for these type of products: requirement of a physician training program; additional FDA post-approval requirements; postmarket surveillance; annual reporting; restriction of the sale of device requirement, to

have the displayed warnings, adverse events on advertising; medical device reporting requirements, submission of annual reports to the FDA.

[Slide]

Review of one of the critical factors is the manufacturing of these products and manufacturing requirements for Integra as well. And, these others, product manufacture in compliance with the FDA Quality System Regulations. The facility is FDA registered, ISO 9001 certified. Pre-approval inspection, prior to approval of the PMA, routine inspections for compliance with Quality System Regulations; annual reporting in the PMA as far as any changes to the manufacturing processes or quality control procedures that don't need to be submitted under a PMA supplement and, of course, PMA supplements.

[Slide]

Just briefly, I want to show again the critical nature of these type of products and why they need to be made available. This is a young patient. This patient was in the clinical trial.

Each patient served as their test and control site. This is a seven-year follow-up. This is the area treated with Integra and this is the area treated with the patient's own skin. You can see this replaces the dermal tissue which grows with the patient.

[Slide]

Another critical factor of this is that the young patient burned the day after Christmas, smoking in a shed with his friend. He actually escaped unharmed and went back in to save his friend. He suffered a 40 percent total body surface area burn, primarily around his lower extremities. He was treated with Integra.

[Slide]

What I want to show you is this patient returned to school in approximately six weeks and was playing sports. This is that patient playing sports just four months after his initial injury. This demonstrates not only the life-saving effects but also the criticality and the improvements in the quality of life of these patients.

[Slide]

Recommendations, the documents to be used for interactive burn and wound dressing submissions, right now there are two excellent draft guidances that are available. The draft guidance that was developed in conjunction with the Center for Devices and Biologics and the Center for Drug Evaluation, which is chronic cutaneous ulcer and burn wounds, developing products for treatment, in June, 2000. Also, the FDA draft guidance for the preparation of an investigational device exemption submission for interactive burn and wound dressings.

[Slide]

Again, I am not going to read everything here due to time constraints, but the basic data from the company: reports of prior investigations, both preclinical and clinical trials, and any clinical trials conducted outside the U.S.A.; description of device; principal mode of action. If the principal component is collagen, the type of information that is required is the type of

collagen tissue species; country of origin; processing; viral inactivation studies; BSE, TSE, risk analysis. If cultured cells are incorporated into the device, complete description of the origin of the cells; methods of separation; manner in which the cells are handled; culturing techniques; any agents such as growth factor used in culturing.

[Slide]

Assurance that the cells are free of transmissible diseases and the type of testing conducted on the cells. Final product testing is to include sterility and mycoplasma, endotoxin, pyrogenicity tests.

[Slide]

Quality control procedures; validation processes; biocompatibility testing with the standard conducted according to ISO 10933, and then additional studies as indicated, such as ADME studies, absorption, distribution, metabolism, excretion and other studies depending on the biomaterial or the cells involved.

[Slide]

Animal models--as we all know, there are no really ideal animal models for evaluating these type of wounds or for burn wounds, but the animal studies selected depend on the type of wound and the claim being sought.

[Slide]

Complete investigational plan, intended use, objectives of the studies, number of patients, duration, description of the study, inclusion, exclusion, methodology.

[Slide]

Pretreatment is very important in these studies, what type of pretreatment; baseline evaluation; wound biopsies; culturing; hypersensitivity screening; preparation of the wound bed and whether it is debridement, irrigation or excision of the wound.

[Slide]

Treatment regimen for the experimental and the control group; descriptions of both the control and experimental treatments; frequency; description of how the uniformity of the control and

experimental treatments will be maintained across investigational sites.

[Slide]

Post-treatment and post-treatment follow-up, both acute and long-term; description of the schedule and the types of studies; lab testing; dressing changes; biopsy of the wound; histological evaluations.

[Slide]

Device effectiveness evaluations. Study endpoints must be clearly defined. Comparisons to standard care; device effectiveness evaluations; wound healing measurements such as validated scales; histology of the tissue.

[Slide]

Very important is time to wound healing; long-term follow-up; evaluation of cosmetic outcome; patient and investigator evaluations of their treatment; standardized photographs and the photographs should be evaluated by a panel of masked evaluators; and wounds should also be evaluated by a panel of masked evaluators; patient

satisfaction and quality of life using a validated measurement tool.

[Slide]

Post-approval requirements--again, a post-approval study, if necessary to obtain additional safety and effectiveness of the device; restriction on the sale; requirement of warnings, hazards and adverse events for labeling and advertisement. Again, there can be requirements for device tracking, and also to include identification codes on the device and labeling and cards given to the patients, if necessary to protect the public health.

[Slide]

Annual reporting, a powerful tool that FDA has for reporting any changes to the device. Physician training, as indicated, and other post-approval requirements.

[Slide]

Conclusion, FDA guidance for industry, chronic cutaneous ulcer and burn wounds, developing products for treatment, developed by FDA Biologics,

Devices. The drug should be finalized and implemented. Products for skin replacement regeneration should remain in the Center for Devices, with consultation from CBER depending on the components. The Center for Devices has the technological experience with evaluating these submissions for skin replacement regeneration.

[Slide]

Integra regeneration template contains no live cellular components. Integra has been regulated as a Class 3 medical device for 20 years. The review of Integra by CDRH has been extremely rigorous. There are no public health concerns with Integra, nor am I aware of any with the other products indicated for skin replacement. Integra has been evaluated since 1982 and marketed for six years with an adverse event rate of less than 0.02 percent. Integra has demonstrated extensive safety and effectiveness data and long-term safety and effectiveness data. CDRH has provided extensive review of burn and interactive wound dressing products and should continue to be the primary

reviewer of these products. Thank you.

MR. BARNETT: Thank you, Ms. O'Grady.

Panel? If there are no questions, then I will call on the next speaker, who will be Ms. Alison Lawton of Genzyme Corporation.

Genzyme Corporation

MS. LAWTON: Good morning.

[Slide]

I am Alison Lawton. I am senior vice president of regulatory affairs and quality systems for Genzyme Corporation.

[Slide]

This morning I would like to talk to you a little bit about Genzyme's experience and Genzyme's comments on the Federal Register notice. First of all, just to give you some background, Genzyme has many therapeutic and diagnostic products. We are currently developing a number of different cellular-based therapies, including such products as autologous cell therapies, cancer vaccines, gene therapies, as well as cellular xenografts. So, we have significant experience in the development of

such cellular products, as well as the manufacturing.

In addition, we have two commercial products. One is Epicel, which I am going to talk a little bit more about today because it fits the definition of the wound healing products that we are talking about today. But I do also want to mention Carticel because Carticel is a second commercial product that we have. You have heard already a couple of speakers this morning actually mention about manipulated autologous cells for structural repair, and this is what Carticel is. Carticel is an autologous chondrocyte product for the repair of articular cartilage. If you look at the strict intercenter agreements and the definitions this, of course, in theory, because of the structural aspect, it would be a device. However, it was designated as a biologic under the guidance.

So, at Genzyme we have unique experience and honor, if you like, to have two different cell therapies, one regulated as a device and one

regulated as a biologic. So, I would like to give you some of our perspective based on that experience that we have.

The other thing that I also want to say is that although at this meeting we are just talking about wound healing products, I do believe that the discussions have much broader implications and that there are going to be many more new, complex cell therapies and products in the future, and whatever decisions are made on these types of wound healing products will have implications in the future products being developed.

[Slide]

Just to start with, to give you a little bit of an overview of Epicel, Epicel is a cultured epidermal autograft. It is autologous keratinocytes which are placed on a petrolatum gauze backing. It is indicated for deep dermal or full-thickness burns in patients with greater than 30 percent total body surface area burns. It is also indicated for congenital giant pigmented nevus.

[Slide]

Epichel was originally developed by the Harvard Medical School in 1998. It was actually commercialized by a company called Biosurface Technologies which Genzyme acquired in later years. But it has been available for patients with serious burns since 1988. In 1997 it was designated as a medical device. In 1998 we applied for, and were given the designation for humanitarian use device based on the fact that we are only treat about a hundred patients a year with this product. It is really supplied just as a service for these severely burned patients.

In February of 1999 we submitted a humanitarian device exemption, and about a year later, actually in January of 2000, we had the opportunity to present to the FDA's Xenotransplantation Subcommittee Advisory Committee because Epichel was also considered to be a xenotransplant product at that time because of the 3T3 mouse-feeder cells that are used in growing the keratinocytes. So, for Epichel it was decided it

would be regulated as a device.

We also have experience with Epicel that it was very clearly a combination product for different reasons. It was a combination product because it was a device plus a xenotransplant product. I do have to say that the review process for Epicel has not been the easiest. It has not been the smoothest process, and one thing that I think I would comment on is that I think it is absolutely critical that whatever happens, you have to define and really define well the processes for joint reviews or for the reviews with leading consult centers as to how these processes will work, and the level of accountability and how that would be managed, not only within the centers of the FDA but also so that it is transparent for the sponsors.

[Slide]

What I would like to move onto now is to talk about specifically the Federal Register notice. The question was asked is there a potential public health concern. You have heard

today that many of these approved products actually provide a public health benefit, and I certainly agree with that comment. However, I don't think that we should lose sight of the fact that because these are living cells, living human cells, there is a potential public health risk. I say "potential" because clearly we have not seen this to date, but we have to take this into consideration in thinking about how these products will be regulated.

The potential public health concern is that of potential transmission of infectious agents. This was actually very clearly outlined and noted in the 1997 draft tissue regulations. It specifically talks about this point, and I think that it actually presents it very nicely in that draft regulation.

Particularly with regards to the potential for transmission, clearly there are a number of sources that could arise from the actual tissue or the cell sourcing itself. It could arise from introduction or cross-contamination during the

process, and that is why the manufacturing aspect, which I will talk about in a little more detail in just a moment, is absolutely critical to the regulation of these products.

Clearly, the level of regulation needs to be commensurate with the risk. As with all these different types of products, we have to make sure that that is the appropriate level. But, for example, with the potential transmission of infectious agents, it may be that it is more important for screening of the donors for an allogeneic product than it is maybe for an autologous product.

Processing is another issue that needs to be considered as to how much the product is manipulated during processing. Do you have multiple products in a manufacturing facility, etc.?

[Slide]

Let me move now to the issue of manufacturing controls. I mentioned that, clearly, the manufacturing controls--and you have heard from

other speakers this morning that these are absolutely critical in particular to minimize this potential risk from infection from adventitious agents.

There are a number of aspects which are standard as far as GMPs which apply to these products just as they do for any other products. But there are also some specific aspects that we need to be thinking about for cell products. For example, you need to make sure that during your manufacturing process that any natural bioburden of those cells is not being amplified during the process.

You need to be sure that there is no cross-contamination during the processing and, in fact, that you are not introducing new potential agents. For example, for auxiliary products you need to make sure that you are not introducing potential adventitious agents. Many of the aseptic processing procedures, environmental controls, patient ID and lot tracking is all, again, to do with preventing contamination of these products.

Finally, one of the other things is the uniqueness of these types of products, often because of the cellular component, the shelf-life is much shorter. It is not your standard months or years. It can be hours, if not days, and often these products are released and given to patients before you even have the chance to get full test results back from, for example, sterility testing. So, again, it just highlights how important the manufacturing controls are during the process.

As far as safety and effectiveness or safety and efficacy of these products, we believe that, as with any product, it is important to prove and to show the safety and efficacy of the product. We believe that this should be done in the setting of controlled clinical trials. We recognize that the agency does need to have a flexible approach. In some cases the standard controlled trials, placebo-controlled trials or even controlled trials may not be applicable; they may not be feasible and they may not be ethical. That is certainly the case, for example, with Epicel.

[Slide]

As far as mode of action and product designation, we believe that you can't separate the fact that these living cells are present in the product. The living cells, whether we like it or not, do release cytokines and other substrates which we believe, in some way, must contribute to the efficacy of the product. Therefore, you can't take that out and separate out.

I would like to give you just one example here. There are some companies who have a current wound healing product that is regulated as a device and they are currently studying the effect of this product on angiogenesis because of the release of these types of growth factors, etc. from the cells. There are other companies who are developing gene therapies or, say, recombinant proteins that have exactly the same angiogenic effect but are being regulated as biologics.

These two things have exactly the same mechanism of action whether they are being released by the cells or whether they are being introduced

as a recombinant protein or in gene therapy. I would ask you to consider is it appropriate, therefore, that they should be regulated in two completely different environments because one is a cell delivering it versus the other's with a slightly different delivery system.

[Slide]

The second part, we believe that the discussion around the scaffold and the matrix or the biomaterial, if you like, really needs to be considered a delivery system for optimizing the fact that those cells are there and playing an important role in the efficacy of these products. Therefore, we believe that there needs to be a consistent approach to all products containing human living cells, and that the living cells themselves, if you like, the cell component should be considered the highest order and based on the fact that the cells are there, that should be the reason as to why and how these products get designated.

We believe that the current products that

have been regulated within CDRH should remain because of the difficulty of switching them. However, for any new cell products and, very importantly, any new indications, for example the example I just gave to you, the angiogenesis example, these should be regulated by CBER. We believe CBER does have the experience of regulating such biological systems. As I mentioned earlier, they also regulate many of the specified products or the other components, such as the cytokines and the growth factors which are often being released by the cell as part of the mode of action.

I mentioned at the beginning of my presentation the issue of Epicel, and I would highlight again that we really need very clear, defined processes and guidances to be issued for how these products will be reviewed. So, if CBER is the main center to regulate these products, how is CDRH going to be involved in the review of the device component? Is it going to be a joint review? Is it going to be a consult? And, let's understand what the accountability and the time

lines are for the process.

The last comment I would like to make is with regards to harmonization. Harmonization, as we all know, is a very important part in development of any product in this day and age. Global development is key. We know that in Europe at the moment the European Commission is currently drafting two new directives with regards to cell therapies, and it looks as though they are moving towards this approach, that if it contains a cell then that will define how it becomes regulated.

I know that this is obviously a discussion for how these products will be regulated within the FDA, but I think it is absolutely critical that the FDA continues to have discussions with other regulatory authorities such as the Europeans and the Japanese, as we do in the ICH process, to be part of this so that anybody, any company developing such products is able to have one approach worldwide. Thank you very much.

MR. BARNETT: Thank you. Panel? If not, I think we are ready for lunch. But before we do

that, just so I get an idea how the afternoon is going to shape up, I would like to have a show of hands if you are not--I repeat not--a scheduled speaker on the agenda but think you would like to speak during our open mike session. Could you raise your hand so I can get an idea of how many people may want to do that? Not many.

All right. We are scheduled for an hour for lunch. I have 11:40. Why don't we make it 12:45? Food is available in the hotel downstairs where you got your coffee.

[Whereupon, at 11:40 a.m., the proceedings were recessed for lunch, to resume at 12:45 p.m.]

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

MR. BARNETT: A few housekeeping details before we begin. Is Dr. Sabolinski here? Yes? One of our other speakers, Dr. Zuckerman, who goes on before you has been delayed. Could I ask you, if necessary, to switch and go a little earlier?

DR. SABOLINSKI: Sure.

MR. BARNETT: Great! Thanks. The second item is that I want to remind you again that we do need copies of your presentation. So, if you haven't done it yet, please leave one at the registration desk outside the door.

The third housekeeping things has to do with parking. I am told that the way to do this is to present your parking ticket at the front desk of the hotel. Pay them there. They will give you your receipt and then you show the receipt in the garage. Apparently, you can't pay the guy downstairs in the garage.

So much for the important stuff. Our next speaker is from Ortec International, and he is Dr. Costa Papastephanou.

Ortec International

DR. PAPASTEPHANOU: I will start and the slides will catch up. I am Costa Papastephanou. I am the president of Ortec International. Ortec is a tissue engineering company involved in the commercialization of a proprietary and patented technology to stimulate the repair and regeneration of human tissue.

Ortec's current focus in is the application of its Orcel, a bilayered cellular matrix to heal chronic and acute wounds. Orcel is composed of a collagen matrix, seeded with allogeneic epidermal and dermal cells. These cells secrete growth factors and cytokines normally found in acute human wounds, and are believed to create an environment that may have a beneficial role in promoting tissue repair.

In addition to having received FDA approval during 2001 for the treatment of epidermolysis bullosa and donor sites in burn patients, Ortec is also pursuing FDA approvals for venous and diabetic skin ulcers and is in the midst

of clinical trials for these indications.

[Slide]

Our purpose in coming before this hearing is to express our strong opposition to any jurisdictional transfer of jurisdiction of wound healing products containing live cellular components from CDRH to CBER.

[Slide]

Orcel has been in clinical evaluation for acute and chronic wounds since 1992, and in commercial distribution since 2001, with no reports of serious adverse events directly related to the use of the product. All the data from our controlled clinical evaluation have been reviewed by CDRH and demonstrate an excellent safety profile. Therefore, we see no need for change in jurisdictional control as it relates to safety and efficacy of the current products under development or in commercial distribution.

In our view, the public is concerned with access to safe and effective treatments for severely compromising wounds arising from a variety

of chronic and acute situations, not with jurisdictional control. These combination products provide an immediate covering that helps reduce the risk of infection, protect against either fluid loss or desiccation, and helps to restore the skin's natural function through promoting and speeding the healing process.

[Slide]

We believe that the approach applied by CDRH under the current regulatory scheme is comprehensive for wound care products, including those containing live cells. CDRH provides adequate protection of the public health from the risks of transmission of communicable diseases and from therapies and products that may be potentially dangerous to the public health.

Since the Medical Device Amendment of 1976, the FDA has been working to clarify the classification of wound care products. Combination wound care products may be composed of any combination of a device, drug or biological procedure. Under Section 503(g) of the Food, Drug

and Cosmetics Act, FDA must designate the center within FDA to have primary jurisdiction for the premarket reviews. The policy, procedures and guidance applied to date by FDA designate the primary jurisdiction over wound care products to CDRH.

Through this process, CDRH has provided guidance and expertise both through the review process and the development of specific guidelines. Their clinical and manufacturing expertise encompasses a myriad of indications, including acute and chronic wounds, orthopedics, periodontal disease and other areas of repair, replacement and regeneration of tissue.

In addition to their ability to regulate biomaterials associated with wound healing products, CDRH has also demonstrated significant knowledge and scientific expertise in the regulation of human- and animal-derived cellular and extracellular products through years of jurisdictional responsibility. CDRH plays a key role in the development and implementation of

critical FDA guidance documents and intercenter agreements that have a direct impact on establishing the safety and effectiveness of combination products containing live cellular components.

These guidance documents adequately address the chemistry, manufacture and control requirements for cell therapy products, including recommendations for labeling claims, outcome measures, clinical trial designs and special considerations for preclinical development and testing.

Specific public safety concerns addressed by these documents include the transmission of infectious diseases, such as AIDS and hepatitis; contamination control, such as mycoplasma; toxicity and immunogenicity. The autologous and allogeneic cells in combination with the device matrix for wound healing, unlike systemic or metabolic cell therapies to treat malignant and infectious disease, create a local environment rich in growth factors, cytokines and extracellular matrices for

wound healing. The clinical concerns regarding this type of wound healing device are more at the local level and center around risk of infection, the transmission of viruses and the potential for any immune response.

To date, we are not aware of any serious public health issue arising from these combination products containing live cellular components. The safety and effectiveness issues have been adequately addressed in the premarket requirements and guidance documents, and adequate controls are currently in place.

[Slide]

The technological advances over the past ten years have made possible progress of combining devices, pharmaceuticals and/or biologics. Such products are likely to increase in importance and numbers over the next few years, and they represent a significant increase in the level of complexity and scientific challenge to CDRH and to the FDA as a whole. Whether these products are regulated as devices or biologics has depended on the primary

intended use of the product. However, there was no clear pathway or guidelines for regulating these products.

The approach taken by CDRH has always included a degree of input from each regulatory center, balancing safety and effectiveness with the desire for timely decisions. These products need to be regulated with an approach that embodies the philosophy of CDRH, one that is least burdensome, predictable, timely, flexible, transparent, interactive and effective. CDRH has historically developed a plan of collaboration with other centers for the evaluation of combination products.

Intended use, not the primary mode of action, should continue to be the clinical factor in determining the jurisdictional control of these products. Wound healing is a complex process, such that all the factors involved and the potential contribution of each factor to the healing process as a whole have not been defined. The wound healing process containing both non-living cellular matrices and living cellular components such as

cytokines and growth factors combine to create a local environment that is conducive to wound healing, repair and regeneration by the host cells. It is extremely difficult to determine which action is the primary since the overall outcome is dependent on the total wound environment.

Since we believe that the intended use is the critical factor that should determine the assignment of primary jurisdiction, the indicators that should be taken into consideration, both in determining the jurisdiction and the appropriate type of premarket approval, should center on the product safety and effectiveness and the FDA's adverse reporting process. CDRH has maintained jurisdiction and responsibility over wound healing products since the Medical Device Amendments of 1976. Even as new technologies have emerged and the complexities of incorporating cellular or tissue engineering components into wound healing products introduced new scientific challenges, CDRH has developed the necessary technical expertise, either within the organization structure of CDRH or

through intercenter cooperation, to meet statutory requirements and to bring new technologies to the market.

In our opinion CDRH has kept pace with the rapidly evolving technologies in wound healing, including a growing number of combination products. Overall as an industry, we have received more than adequate guidance from CDRH in regard to addressing the challenges of our technology, including critical technical expertise related to manufacturing, safety testing and well-designed, controlled clinical evaluations. The critical success factors associated with our commercialization are directly related to the oversight and guidance provided by CDRH.

[Slide]

Again, let me emphasize that the critical factors that should determine the jurisdiction and responsibility of these products should be driven by the indication for use and the experience and expertise associated with risks presented to the public health by the clinical use of these

products. CDRH must remain the lead center associated with the jurisdiction and control of these products in order to assure the continued flow of safe and effective new technologies in the wound care portfolio to better serve the public.

I just want to reiterate something that Advanced Tissue Sciences said earlier, if it isn't broken, why try to fix it? Certainly more importantly, if it is working, let's not break it. Thank you for your consideration.

MR. BARNETT: Thank you, Dr. Papastephanou. If there are no questions from the panel we will go to our next speaker, who is Dr. Vincent Falanga, from Boston University.

Boston University

DR. FALANGA: Thank you, and thank you for giving me the opportunity to voice my opinion about this subject.

[Slide]

I think we have heard from some of the products that are on this list. I am going to actually make my presentation focused on one

particular product with which I have had the largest experience, and that is Apligraf, because I was involved in the clinical trials leading to FDA approval for the venous ulcer and then diabetic ulcer indication.

I am a clinician and I like to think that today I am speaking on behalf of my patients. I believe that the tissue-engineered products really--this is probably the dilemma that we face--present a class by themselves, defying easily available definitions and, therefore, presenting very tough regulatory issues. But as far as I can tell, certainly from the literature and most definitely from my own practice, from the time that they became available commercially they have proven safe as presently regulated.

It is my belief that by histological findings they actually act as implants. They are generally temporary. They don't last in the wound for months. I think that they provide a scaffold for epidermal migration and for the migration of other cells.

This is an interesting point, and I think it is part of the confusion that we face, that they definitely can be shown to produce cytokines and growth factors, particularly when these constructs are injured or manipulated. However, we should be very careful that this particular property of these constructs does not lead us to think that that is their mechanism of action. I think that is a very important point. They all produce some cytokine profile but that is not how they work, in my belief.

[Slide]

As I said, I will make most of my presentation focused on Apligraf but I hope that my comments will also extend to the other useful constructs that have been discussed today. This particular device is Apligraf. This is the histology of it compared to human skin. Like a suitable device, it can be manipulated, as can be seen, and then it can be applied to the patient.

[Slide]

The reason I think they really do work as

a device and really as a scaffold is going to be shown in the next few slides. This is a venous ulcer. As you can see, the edges are very steep which, to a clinician, means they are not moving. But once this becomes activated and ready for healing, the edges of the wound become flat and the epidermis begins to migrate. So, our view is that there is something wrong with the matrix of this wound, and perhaps that is how debridement works. You can see histologically that this is the wound, here; this is the epidermis and there is a lot of epidermis at the edge. I don't know if you can see it in the back, but you can see that there is what we call acanthosis, accumulation of epidermal cells and, yet, they are unable to migrate. Really what is needed is a scaffold that will allow or facilitate the epidermis to migrate. Perhaps the matrix is wrong and there are a lot of theories as to why that would be the case.

[Slide]

These are the kinds of problems that we face in the clinic. I certainly wouldn't want the

field to become more complicated, and I want these products to be available to my patients. This is a patient who is in her 70s and has suffered from this for a long time. We are debriding it and then the construct is being applied to the wound. What I am going to show you is the logical evidence that it is acting as a scaffold.

[Slide]

Here is the wound, and here is the construct. You can see here that the epidermis now has begun to migrate over the construct. It is acting as a scaffold. Interestingly, although it is a bilayer construct, the epidermis is somehow removed very quickly and then the endogenous epidermis begins to migrate over that scaffold.

[Slide]

You can see it at a higher magnification here in a different part of the wound. This is happening between 7 and 14 days after the implantation of the device. Here is the remnant of the construct, and here is the epidermis moving over the device.

[Slide]

Here is another example where you can see very clearly that this is part of the Apligraf or the construct and the endogenous epidermis really likes that scaffold and is migrating very nicely to cover the wound.

[Slide]

It is not just for the epidermis. I presume that there are other cell types that find the construct suitable. Here is an example. This is the remnant of the Apligraf and here is the tissue that has begun to come in contact with the construct.

[Slide]

As I said at the beginning, the fact that some of these constructs produce cytokines and growth factors should not lead us into the idea that necessarily that is how they work. We now have some indication, and actually it is not preliminary because we have repeated this several times, that if you take, in this case, Apligraf and you take punch biopsies of it and place them in

culture--actually, this just shows two pieces in each dish; we use different culture media and that is why the color is different, but in these dishes, if you put other cell types at the bottom so that the bottom will be coated, let's say, by fibroblasts and then you put in these floating discs, if you will, or we have actually used situations where they are in close contact with the monolayer at the bottom of the well, we have been unable to demonstrate that they can increase the proliferation of the fibroblasts.

[Slide]

This is shown here. On the Y axis is DNA synthesis as a measure of proliferation of cells, of fibroblasts that are at the bottom of the well. Here is the control with only the media. If you add ten percent fetal-bovine serum, which is a standard way to reconstitute media or to add to media, you can see that you get nice stimulation. So, that is your positive control. But you can see that the Apligraf was unable to stimulate the fibroblasts.

What I am saying to you is if it really was working by means of creating this wonderful milieu of cytokines and growth factors, then you would have seen an increase in this. The idea that it works by cytokines and growth factors goes against my clinical experience with many, many clinical trials in which we tested growth factors in chronic wounds and have found them to be ineffective.

[Slide]

I beg the government really to reconsider any reclassification of the regulation of these products if it is going to interfere or make it more difficult for my patients to obtain these products. They have changed my practice. They have made it much easier to deal with difficult problems.

Here is a patient with a very large venous ulcer that healed with this product very nicely. She was not healing at all before for at least two years.

Here is a baby with epidermolysis bullosa.

This slide is by courtesy of Dr. Falabella, from the University of Miami. This is a young child with denuded skin and these types of products can make a big difference to these children both in terms of pain and in accelerating the healing. Anything that is not based on scientific evidence that will change the regulation of these products might make it more difficult for these patients to receive them.

[Slide]

Here is another patient of mine with multiple myelomas, undergoing bone marrow transplantation, but before then he developed this large wound on his chest.

[Slide]

I want to show you how these products can make a big difference in our patients and, therefore, we have to think very carefully about anything we do and any unintended consequences of our decisions.

[Slide]

Here he is. The product has been applied.

After that was done, after the device was placed, complete healing occurred and made his life a lot easier and increased his quality of life.

[Slide]

This is a slide that I showed earlier when I said we were applying this to these difficult patients, and you can see that several months later she is still healing. I think if something were to work by the release of cytokines, especially since we know that they don't last for months in these wounds, it wouldn't have been so. So, I think it is the facilitating activity of the implant activating the epidermis so that now she is healing.

[Slide]

In conclusion, I believe that the exact mode of action of bioengineered skin devices is not clear, but a decision to regulate them as biological agents should be based on evidence. The fact that most of these devices are able to produce cytokines and growth factors does not mean that this is how they work. In fact, we have data

showing that at least one bilayer skin substitute, such as Apligraf, may work as a scaffold and facilitator of epidermal migration and, indeed, is not able to stimulate cellular proliferation in the assay system that I have shown you.

I believe that these innovative products have made a very significant difference in how we help our patients, and we are very concerned that any additional layers of regulation, unless they are based on safety issues and scientific evidence, will be detrimental to present highly effective products and will probably discourage the development of new ones. Thank you.

MR. BARNETT: Thank you, Dr. Falanga. If there are no questions from the panel, we will go to our next speaker, Jae Lee of the Patient and Consumer Coalition.

Patient and Consumer Coalition

DR. LEE: Good afternoon, and thank you for permitting me to make a few comments.

I am Dr. Jae Lee, and I am speaking on behalf of the following members of the Patient and

Consumer Coalition, International Union, United Auto Workers, National Women's Health Network, the National Center for Policy Research for Women and Families, the Center for Medical Consumers, the TMJ Association and the Title II Community AIDS National Network.

The Patient and Consumer Coalition recognizes the great importance of these products to millions of patients with severe burns, diabetic skin lesions, work and accident-related injuries and decubitus ulcers. This is an important issue for consumers, and the implications for how the FDA functions as a scientific and regulatory agency is also quite important.

We consider it imperative that any new wound healing combination product undergo a thorough and comprehensive evaluation for safety and efficacy before coming to market. In addition, any center with jurisdiction over these products must ensure that adequate postmarketing surveillance is performed to monitor adverse events. In determining jurisdiction over these

combination products, we believe patient safety must have priority over all other considerations.

The Patient and Consumer Coalition believes that assignment of jurisdiction over new wound healing combination products should be based on the unique characteristics of each product. The traditional assignment of these combination products to the Center for Devices and Radiological Health should play no significant role in determining jurisdiction over future products. Jurisdiction should be assigned, instead, to the center that is best equipped to evaluate the safety and efficacy of each new combination product.

The primary mode of action of a new combination product serves as a useful guide in assigning jurisdiction. In evaluating the primary mode of action, the following questions must be asked: One, which component provides the greatest therapeutic benefit for the patient?

Two, which component, if it fails or is defective, poses the greatest risk to patient health and safety?

Three, which component has the longest-lasting impact on patient health?

Four, which component interacts most closely with the patient's own tissues and cells?

Five, which component, if any, is permanently implanted into a patient?

Six, which component must be thoroughly discussed in order to obtain true informed patient consent?

We feel that in evaluating the primary mode of action of any new combination product, the patient's perspective must be given the highest priority.

In assigning jurisdiction over new combination products, priority must always be given to patient safety over rapid product approval. The Patient and Consumer Coalition believes that thorough premarket evaluation of combination product safety and efficacy will benefit patients far more than rapid approval of new products. The center that is assigned jurisdiction over a new combination product should commit to placing

patient safety above industry demands for rapid evaluation and approval.

The Patient and Consumer Coalition believes that the center assigned jurisdiction over a new combination product should have adequate in-house expertise to evaluate the product based on its primary mode of action. For example, if the primary mode of action is through the combination product's biologic component, the center assigned jurisdiction should have adequate in-house expertise in the biological sciences. Not only would such in-house expertise permit a more thorough evaluation of new products, it would also allow a center to more readily address important public safety concerns, for example, bovine spongiform encephalopathy.

The Coalition opposes the use of any outside consultant in the evaluation of new combination products if these consultants are chosen and/or paid for by industry. Such outside consultants are subject to intolerable financial and professional conflicts of interest. Adequate

staffing with in-house experts should minimize or even eliminate the need for such outside consultants.

Once a new combination product is approved for market, the center assigned jurisdiction should require manufacturers to perform comprehensive postmarket surveillance studies. It is not reasonable to assume that all public health concerns can be addressed during the premarket review process. We have heard that assertion made more than once today.

The center should devote sufficient resources and personnel to closely monitor adverse events. Ideally, the center assigned jurisdiction should have sufficient regulatory authority to compel manufacturers to complete all required postmarketing surveillance activities. All centers with jurisdiction over combination products should be required to report to Congress, on an annual basis, the rate of completion and status of required postmarket surveillance activities and any action taken by the center against companies that

failed to fulfill these requirements.

In summary, the Patient and Consumer Coalition believes that patient safety should have priority above all other considerations when assigning regulatory jurisdiction over new combination products. Thank you.

MR. BARNETT: Thank you, Dr. Lee. Let me ask whether Dr. Zuckerman has arrived. Is she here? If not, let me ask Dr. Sabolinski if he would take her place. I would appreciate that. The next speaker then is Dr. Michael Sabolinski of Organogenesis, Inc.

Organogenesis, Inc.

DR. SABOLINSKI: Thank you for the opportunity to comment at this open hearing.

[Slide]

My name is Michael Sabolinski, and I am presenting on behalf of Organogenesis, located in Kent, Massachusetts.

[Slide]

We are the manufacturers of Apligraf, living bilayered skin substitute, consisting of an

epidermal layer formed by human keratinocytes, with a well-differentiated stratum corneum; a dermal layer composed of human fibroblasts and a bovine type one collagen lattice; matrix proteins and cytokines found in human skin, and we do not contain Langerhans cells, macrophage, lymphocytes, blood vessels or hair follicles, and Apligraf is sold in the United States by Norvadis Pharmaceuticals Corporation.

[Slide]

This shows a photograph of Apligraf being removed from its container. Apligraf is a single entity. It is 75 mm in diameter and 0.75 mm in thickness, and it is applied directly onto the wound bed.

[Slide]

Apligraf's regulatory pathway is shown in this slide. In 1985 Organogenesis was established to commercialize its lead product, Apligraf. In 1986 FDA designated Apligraf as a device. In 1987 the IDE was submitted. In 1995 the PMA was submitted. In 1998 the PMA was approved for the

treatment of venous leg ulcers, and in 2000 a PMA supplement was approved for the treatment of diabetic foot ulcers.

[Slide]

Apligraf's approved indications--Apligraf is indicated for use with standard therapeutic compression for the treatment of non-infected partial and full-thickness skin ulcers due to venous insufficiency of greater than one month duration, and which have not adequately responded to conventional ulcer therapy.

Apligraf is also indicated for use with standard diabetic foot ulcer care for the treatment of full-thickness neuropathic diabetic foot ulcers of greater than three weeks duration, which have not adequately responded to conventional ulcer therapy and which extend through the dermis but without tendon, muscle, capsule or bone exposure.

Apligraf underwent a careful regulatory review. Regarding manufacturing controls, these are the tests, maternal donor screening and testing; master cell bank and working cell bank

testing; qualification of reagents, including animal-derived materials; aseptic processing controls; compliance with Quality System Regulations; Good Manufacturing Practices; in-process testing and final release specifications, such as sterility and histology.

[Slide]

This slide shows some of the microbiological safety testing performed. On the left are shown tests for maternal blood; on the right, tests for cell banks. You see adventitious pathogens, such as HIV, hepatitis A, B, C, cytomegalovirus and other expected pathogens that must be ruled out and carefully screened for.

[Slide]

Special emphasis in wound healing should be applied to the evaluation of clinical trials. Randomized, controlled clinical trials comparing Apligraf to the standard of care to establish safety and efficacy were performed.

Some of the regulatory hurdles unique to wound care--definition of the primary endpoint and

evaluation of that endpoint of complete wound closure. These are procedural-based studies, akin to surgical type of studies where the patient population numbers are limited: the choice of active control groups; an unmasked study design using skin compared to routine care; the use of photographs and third-party review; adverse event reporting and immunology, both humoral and cellular-based immunology.

It should be noted that comparators for wound healing studies are devices. In addition, a very important component of clinical trial design and review is the use of appropriate statistical techniques to account for factors influencing wound healing, such as outcome survival analyses, the Kaplan-Meier survival curve, and other multivariate regression models such as the Cox's proportional hazards regression model and logistic regression. These are important in order to correct for factors that can influence wound care that may not have been evenly distributed between treatment groups, study and control groups, that are mathematically

correct for in multivariate regression.

[Slide]

Public health considerations--there are no public safety concerns that exist to support a jurisdictional change. Apligraf has shown a strong safety profile. Over 50,000 patients have been treated with Apligraf since its approval in 1998. The incidence of medical device reports is less than 0.01 percent. Adverse events allocated to wounds are infection, cellulitis, edema, erythema and inflammation, and these adverse event reports are comparable to standardized care or non-interactive wound dressings.

[Slide]

We believe that public health considerations are adequately addressed by FDA policies and practices, such as the development of good guidance documents, for example, chronic cutaneous ulcer and burn wounds, developing products for treatment, developed by all three centers, and also Part 1271 of the Code of Federal Regulations for good tissue practices, human cells,

tissue and cellular and tissue-based products.

[Slide]

Dr. Falanga alluded to the complexity of wound healing. Wound healing is a complicated process. Acute wound healing involves a complex cascade of overlapping events at the wound site. In chronic wounds there is a failure to progress through a normal, orderly and timely sequence of wound repair. In any case, it is not caused by a single event.

[Slide]

Apligraf acts as a single entity and its structural attributes, by both structure and function, act as a whole. Cellular components are integrated into the acellular matrix, resulting in a cellular wound dressing with specified dimensions. Apligraf is released based on histological criteria of the structure and functional attributes. It is applied in one unit to a local wound site. Apligraf acts as a wound covering and performs the barrier function of skin. Apligraf also produces cytokines found in normal

human skin. The components come together to work as an integrated unit.

[Slide]

This slide shows a photomicrograph of a routine hematoxylin-eosin stain of Apligraf. From top to bottom, you see the stratum corneum, which is a non-living protective barrier; the epidermis, which is a living cellular entity; and then type one collagen with fibroblasts in the dermal component of the product. That product is applied so that the dermis contacts the wound bed.

[Slide]

Apligraf has a localized effect. Systemic adverse events have not been attributed to Apligraf. Apligraf's physical properties provide immediate wound coverage and barrier function. It has a localized effect on wound healing. It does not affect healing of non-contiguous ulcers. There is no evidence of absorption or metabolism of Apligraf and, in summary, Apligraf's total therapeutic effect is localized.

[Slide]

Regarding mode of action, cells make the final structure of Apligraf possible but cannot be separated either physically or functionally from the matrix. One is unable to determine the quantitative contributions of components of Apligraf, and we are unable to determine a single mode or primary mode of action of Apligraf.

[Slide]

Factors for jurisdictional assignment-- since it is not possible to determine the primary mode of action, the following factors should be considered: The intended use. Wound healing is unique. Secondly, overall structural and functional properties of the product as a whole. Safety testing of components; manufacturing controls; and special emphasis placed on wound healing studies, randomized, controlled clinical trials; finally, postmarketing adverse event reporting. The current regulatory paradigm in place under CDRH is effective. CDRH placement does not preclude intercenter collaborative review.

[Slide]

CDRH regulation of wound healing products-
-jurisdiction was established by the Medical Device
Amendments of 1976. CDRH has developed expertise
and knowledge in the issues unique to wound
healing. FDA guidance documents address issues
regarding wound healing products with living cells.
Patients and healthcare products have benefited as
additional wound treatment options have become
available, and CDRH has implemented and
consistently applied regulatory controls to ensure
only safe and effective products are introduced to
market.

[Slide]

Our conclusion is that maintaining the
current regulatory structure with wound healing
products assigned to the jurisdiction of CDRH will
assure adequate review of new technologies,
continue to protect the public health and advance
the field of wound care. Thank you.

MR. BARNETT: Thank you. Any questions
from the panel? If not, let's continue in the same
order as the speakers are listed on the agenda and

if Dr. Zuckerman arrives later, we will put her on. The next speakers will be Dr. Stephen Noga and Scott Burger, from International Society of Cellular Therapy.

International Society for Cellular Therapy

DR. NOGA: Good afternoon.

[Slide]

I am Steve Noga. I am here in the capacity as President of the International Society for Therapy, formerly known as ISHAGE, the International Society of Hematotherapy and Graft Engineering. Maybe through this talk it will become apparent why we changed our name. I also have with me Scott Burger, who is here in his capacity as a member of the executive board of ISCT, as well as editor for the newsletter for the society. We are very happy to be here to give our opinion on this particular topic.

[Slide]

Essentially, of course, there are several organizations but our particular organization represents scientists, technologists and regulatory

individuals within the evolving field of cellular therapy. This includes all aspects of cellular therapy, tissue-based therapies and gene manipulation and gene therapy.

Along with our society, of course, there are several other societies which we have common interests with, and these, of course, include the American Association of Blood Banks and the American Society of Blood and Marrow Transplantation.

Of course, as we started, like many societies, we started mainly with hematopoietic transplantation but in the field of stem cells and embryonic stem cell research this all started moving forward into cellular therapies and, hence, the name change for our society.

Scott, you are going to talk over the next few slides.

DR. BURGER: Thank you.

[Slide]

Although the focus of the hearing today is certainly on combination products that involve

wound healing, the skin and skin-derived tissues in combination with non-living matrices, certainly it is abundantly clear that the regulatory structure that arises from today's discussion and eventual decisions will have much broader implications on a much broader range of therapies, certainly, a range of very similarly defined combination products involving a very diverse range of types of cells in combination with non-living matrices. A range of such therapies is currently being developed. Some of these include encapsulated pancreatic islet cells, hepatocyte-based liver-assist devices, mesenchymal or mesodermal cell-based structural grafts, as well as others. So, the conclusions from today's discussions certainly have a broad range of implications for how future cell- and tissue-based therapies develop.

[Slide]

Certainly, appropriate reasonable regulatory oversight is needed, I think we are all in agreement, for both elements of such combination products, both the living cellular element as well

as the non-living matrix. It would seem that the regulatory structure that is most appropriate should perhaps be based on the element that is most in need of control, which element, therefore, is the most complex, the most critical and most prone to variability; which element most critically affects the patient's long-term outcome; which element is most vulnerable to effects of environment.

This certainly becomes, if anything, more complex if, in addition to genetically modified cells in the future, the matrix itself may be in some respect genetically modified or may be derived from genetically modified material. Although that is not the specific focus today, I think it is wise to bear in mind that both elements have the potential to involve some degree of gene modification.

[Slide]

The non-living matrix certainly is complex in nature or can be complex in nature, but almost certainly its basic safety profile is more readily

established than the living cellular element. The safety, purity and potency testing that one would use is certainly more likely to use established analytic methods when examining the non-living matrix as opposed to the live cellular element.

Perhaps more importantly, consistency is more readily obtainable when dealing with a non-living matrix. Lot sizes are liable to be larger. This is something that is amenable to an extremely rigorous degree of biochemical characterization.

[Slide]

By contrast, the living cellular element can certainly be expected to be more complex and difficult to control. Safety, purity and potency, really the cornerstones of product characterization testing in the current paradigm, will be more difficult to evaluate and may require development and validation of novel analytical methods. This is not at all uncommon in cell therapies as they exist today. Manufacture of a living cellular element may require very extensive, complex cell and tissue engineering approaches and perhaps gene

modifications. Perhaps most challenging of all is the limited availability of test samples. For autologously derived products the lot size sometimes is one patient, one dose, as we know. This may continue to be unique to each patient in some limited number of applications.

[Slide]

So, the basis for the regulatory approach, it would seem, involves a focus on the living cellular element as the most critical element, the element most in need of control. Cell, tissue and gene-based therapies currently are regulated by CBER which has extensive and very successful experience regulating biological products; experience, and very successful experience in the unusual issues that are specific to cellular therapies, as well as very early experience in hematopoietic cell matrix devices, some of which have already been through the CBER regulatory pathway.

There are established relationships with CBER and a number of experts in the field not only

of hematopoietic cell therapy but other forms of cell therapy as well. With this, I think I will turn it back over to Dr. Noga, who will discuss the specific recommendations.

DR. NOGA: This was discussed with the executive committee of the International Society for Cellular Therapy, and these are the specific recommendations of the committee.

[Slide]

We recommend that CBER serves as the primary agency for these combination products. However, having said that, we believe that the full use of CDRH expertise in the device field must be assured. Certainly, there is example for this in the productive and valuable cooperative that has been established between CBER and CDER.

One way to accomplish this, and of course not the only way, would be to have two product reviewers for IND applications for combination products, one from CBER who would provide expertise on biologic products, and CDRH having one who would provide expertise on non-living support matrices.

You have heard similar things said today in terms of consultants and this is just our way of thinking about it.

Certainly, one would hope that there would be representation as the organizational structure comes together for the new CBER Office of Cells, Tissues and Gene Therapy, having CDRH in some way associated or part of this, especially when it comes to combination products.

[Slide]

Continuing with the specific recommendations, we believe--and many of you may recognize this, this is an FDA chart here--that the continued step-wise approach used in regulation of cell therapies should continue. Many of us in the field feel that this is quite necessary, especially when one starts with preclinical level studies and they are advanced through Phase I and more complex Phase III trials which involve more patients. Certainly, in no way should safety in any way be compromised, but certainly there are different levels of control that are put in place as one

moves up this phase ladder. In so doing, these are our recommendations. We are not going to take it any further than that. Thank you.

MR. BARNETT: Thank you, gentlemen.

Questions or comments from the panel? If not, let's continue along the same line on the agenda. Our next speaker will be Dr. Steven Boyce, of the University of Cincinnati.

University of Cincinnati

DR. BOYCE: Good afternoon, and thank you for the opportunity to make this presentation.

[Slide]

I am Steven Boyce. I am trained as a cell biologist and I currently hold positions as associate professor in the Department of Surgery at the University of Cincinnati, and senior investigator and director of the Department of Tissue Engineering at the Shriners' Burns Hospital in Cincinnati. As founder and President of Cutanegen Corporation, a biotechnology development company, and as an ad hoc reviewer for the advisory panel to the General Plastic Surgery Devices Branch

of CDRH, for more than 20 years I have conducted preclinical and clinical studies on a combination of cultured skin cells and biopolymers for prospective treatment of skin wounds.

Clinical studies have been conducted under investigational device exemptions for more than ten years. These studies and those of numerous other academic and corporate laboratories have responded to the extensive medical need for management and healing of skin wounds.

My remarks today are my professional opinions and my understanding of this field based on my training and experience but are not represented to be accurate interpretations of FDA policy, of regulatory jurisdictions of existing products or to be all-inclusive or exclusive.

[Slide]

The extensive medical needs for wound closure may be divided into three main categories: acute emergent as occur in burns over large total body surface areas or toxic epidermal necrolysis; acute elective as occur in reconstructive surgery;

or chronic elective as occur in skin ulcers of multiple etiologies. And, two subcategories, full-thickness which usually require grafting with split-thickness skin to accomplish wound closure, and partial-thickness which usually will close spontaneously if kept clean and protected with conventional dressings.

[Slide]

Medical risks associated with these categories of wounds are proportionate with the magnitude of the injury and the consequent compromise of the protective functions of skin. If medical risks were scale from high to low, factors contributing to high risks would include skin wounds with emergent etiology, great magnitude, full-thickness depth and associated injury or disease.

[Slide]

To emphasize this point, data from the 2002 report of the National Burn Repository show mortality from burns increases from less than one percent of patients with burns of less than ten

percent TBSA to about 67 percent of patients with 80-90 percent burns. Conversely, the predominant majority of patients with chronic wounds may die with a chronic wound but will not die from the chronic wound.

[Slide]

In response to the variety of medical needs and relative risks, multiple approaches have been designed, tested and implemented to restore the structure and function of healthy skin. Because healthy skin consists of two main anatomic compartments, epidermis and dermis, replacements for each of these components have been designed and tested. Although healthy skin provides a multitude of structures and functions for the human body, the essential properties of stable wound closure are restoration of the three Bs, epidermal barrier, basement membrane and blood supply in stable connective tissue.

Healthy epidermis consists almost entirely of cells with minimal extracellular matrix, whereas natural dermis is predominantly matrix with low

densities of cells. Consequently, common approaches to replacement of epidermis have involved cells without matrix, and delivery of a dermal substitute has included acellular polymers from either biologics, such as collagen or synthetics such as PGA and PLA sources with or without cells. In all cases, the polymers are degradable type which have been regulated historically by CDRH.

Furthermore, if cells are contained in the therapy they may be from autologous or allogeneic sources, with autologous cells being able to persist indefinitely after engraftment and allogeneic cells being lost from the treatment site by degradation.

[Slide]

This table summarizes the Cincinnati skin substitute and some products approved for treatment of skin wounds that are acellular or cellular in combinations of polymers and cells. The table is not represented to be all-inclusive or exclusive.

Depending on the magnitude and depth of

the skin wound, either allogeneic or autologous cells may result in permanent closure of an open wound. For example, combination materials containing allogeneic cells such as Apligraf have been demonstrated to promote closure of chronic wounds of unlimited size, but allogeneic cells will not close extensive full-thickness burns. At present, only autologous cells can provide direct structural and functional restoration by transplantation to the disease site, whereas allogeneic cells act indirectly to deliver cytokines and extracellular matrix that stimulate healing by autologous cells of the recipient.

In either case, where living metabolically active cells are applied, the mechanisms of healing are clearly biologic. The biologic contribution to the mode of action of a combination material can be easily quantified and controlled in preclinical studies that compare the combination material to the acellular vehicle.

Acellular materials alone have been demonstrated to promote dermal repair by

recruitment and ingrowth of surrounding tissue, or by combination with a split-thickness skin autograft. However, the composition of the material may be derived from processing of a natural tissue, such as Aloderm, or by extraction of purified components that are fabricated with specific structural and biochemical characteristics that can be distinguished from the natural tissue, such as Integra. The former is considered a processed tissue, while the latter is considered a medical device.

[Slide]

The Cincinnati model of cultured skin substitute has been used successfully to treat and close burns of greater than 50 percent total body surface area in dozens of patients. This demonstrated a clinically significant reduction of donor site requirements to complete wound closure. At the time of surgery, material consists almost entirely of cells, as shown in the lower right panel, and acts by delivering to the wound functional epidermal barrier, basement membrane and

angiogenic factors that stimulate vascularization and biological engraftment of the transplanted cells within five days after surgery.

[Slide]

Culture of cells with a polymer and permissive conditions also allows the development of basement membrane in vitro, as shown in these micrographs. Immunostaining for basement membrane antigens, collagen-7 and laminin-5 demonstrate high fidelity of the natural bond between epidermis and dermis of natural skin, on the left, and the skin substitute, on the right, that brown line.

[Slide]

The clinical relevance of basement membrane formation is dramatized by a case of a child with an 80 percent burn who was treated with Epicel at another hospital until he was transferred to the Cincinnati Shriners' Hospital for definitive care.

The left upper panel shows the effective treatment of wounds on the leg with the Cincinnati skin substitute, with no blistering or secondary

loss of the healed skin. In contrast, sites treated with Epicel blistered extensively, as shown on the lower left panel, and resulted in extensive open wounds, as shown in the right panel.

This patient is currently planned for complete resurfacing of the Epicel sites with the Cincinnati skin substitute. This case emphasizes importantly the greater efficacy of a combination of skin cells with a polymeric delivery vehicle compared to epidermal cells alone. Yet, the combination material in Cincinnati is considered a Class 3 significant risk device under regulation of CDRH, with mandatory multicenter studies, and Epicel, as we have heard earlier, is considered a humanitarian use device with no requirement for performance or review by FDA of multicenter studies.

[Slide]

The clinical efficacy of the Cincinnati skin substitute results almost entirely from cellular processes that at present cannot be duplicated by acellular chemical reactions

performed in the laboratory. The effectiveness of this material reduces greatly the life-threatening risks of extensive full-thickness burns by restoration of the protective functions of healthy skin, as shown in the survivor of greater than 90 percent total body surface area burn.

[Slide]

Comparative clinical studies of this skin substitute to split-thickness autograft have demonstrated rates of engraftment that are not statistically different, as shown in the left plot, and a definitive benefit of reduction of donor skin has been demonstrated by expansion ratios of about 65 times the area of the donor skin versus a maximum of 4 for autograft.

[Slide]

Optimal results for wound closure and skin pliability have been obtained by combination of this skin substitute with a dermal substitute, Integra, most probably because Integra generates a uniform base of vascularized connective tissue that promotes engraftment and reduces formation of

granulation tissue. If this graft base is closed with functional epidermal barrier, inflammatory process that generates scars is inhibited and the resulting skin is smooth, soft and strong.

[Slide]

The same benefits have been demonstrated in a limited number of cases of burn scar reconstruction after pretreatment with cadaver allograft.

[Slide]

For treatment of giant congenital nevus, which also may involve large total body surface areas and require full-thickness incision followed by closure with autologous skin grafts, in this case, this patient was treated previously with autograft on the left back. This patient was treated subsequently with the Cincinnati skin substitute to reduce morbidity from harvesting of donor skin.

[Slide]

Engraftment was rapid and almost complete on postoperative day 15, with no regrafting and an

outcome virtually identical to autograft at one year, in the right panel.

[Slide]

This material may also be prepared with allogeneic cells which have been used successfully to treat chronic wounds. This is a diabetic leg ulcer.

[Slide]

Overall, experience and data generated with the Cincinnati skin substitute has shown that it conserves or eliminates the donor skin for wound closure; has virtually no blistering or minimal regrafting, and produces minimal scar. However, the past and current regulation of this combination of cells and matrix is considered a Class 3 device, under the jurisdiction of CDRH.

[Slide]

The collagen-based substrate used in this material is virtually identical in composition and performance to several kinds of implantable collagen materials that are known to be very safe and efficacious. Yet, the substrates used in the

combination material cannot currently be approved with a 510(k) mechanism. If the substrate were not combined with cells, most probably it would be considered a device of low risk due to the extensive experience and known safety and efficacy of similar materials. However, because there is no predicate it is considered a Class 3 device which requires performance of multicenter studies before marketing approval.

[Slide]

In addition to the relative risk of disease etiology described above, risk may result from the sources of starting materials and processing of the proposed material. For autologous tissue, the FDA guidance on minimal and manipulated autologous tissue for structural repair requires assurances of safety by facilities' registration and processing controls, but multicenter clinical studies are not mandatory.

However, FDA's MAS guidelines may not make adequate considerations of the risks associated with loss of efficacy from isolation, proliferation

and implantation of cells without a matrix. Combination materials for skin repair with autologous cells may provide greater fidelity to native skin by providing both epidermal and dermal components and by regenerating epidermal barrier basement membrane and stimulation of vascularization. The development of functional phenotypes increases skin repair and decreases risks to the patients. But FDA has historically considered the combination materials to have greater risk than grafts of single cell types. Under the MAS guidelines clinical comparison of isolated cells to the standard of care may not be required.

In my opinion and experience, the greater anatomic and physiologic fidelity to natural skin of combination materials, such as the Cincinnati material, increases the benefit to risk ratio for patients more than single cell types without a matrix, such as Epicel. As stated above, if the composition of a device matrix is similar to an existing approved material, then the matrix

component should be reviewed under a 510(k) mechanism because its composition and performance are predictable and of limited risk.

[Slide]

From this perspective, combination materials made with autologous cells should be able to follow the general path to market that is permitted by the MAS guidelines, which is under the jurisdiction of CBER, with a parallel 510(k) review of the matrix by CDRH. Regulatory requirements that extend further than this result in unnecessary delays to entry of new therapies into clinical care without identification of additional risk, except the lack of a precedent in clinical practice. These delays can result in mortality and morbidity to patients.

This flow diagram summarizes the suggested jurisdictions of CBER and CDRH for combination products with autologous cells. So, generally the MAS guidelines with process controls and then development of release criteria and matrix cleared by CDRH.

[Slide]

If polymers or cells are derived from allogeneic sources, the standards established by the American Association of Tissue Banks have provided for conditions of tissue harvesting, processing and tracking, optimal assurances of safety from disease transmission and facility accreditation. These standards, together with FDA's requirements for determination of donor suitability, facilities' registration and inspection, and the developing good tissue practices provide a very positive benefit to risk ratio to recipients of transplanted tissues from allogeneic sources.

Historically, these requirements have been sufficient to allow release of tissues for transplantation without the need for premarket approval or multicenter study. However, if additional processing of tissues occurs to isolated, derived and acellular or cellular component from the allogeneic tissue, then the additional processes may be subject to review to

ensure that biological, chemical or physical risks are not introduced from the process. Furthermore, those processes may denature or delay the structure and function of the original tissue to an extent that compromises its efficacy. Demonstration that processing of tissues does not introduce risks or degrade efficacy may be advisable to ensure that the process material provides the safety and efficacy of the natural tissue. These assurances can be provided by direct comparisons between the processed tissue and the natural tissue in preclinical studies to determine whether or not efficacy is maintained.

In comparison, current FDA standards for materials containing living cells combined with a matrix also require assurances of safety. Because most of the combination materials for skin repair have no predicate and have been considered devices, they have been classified as Class 3 under CDRH. Although the assumption that the combination materials are high risk provides a conservative position that may provide maximum protection to

patients, without determination that a risk from the therapy actually exists, this conservative position may reduce the availability of the therapy to patients who are at greater risk from disease conditions such as extensive burns.

The Class 3 device designation of CDRH requires demonstration of clinical efficacy in multicenter studies to gain approval and CGMP manufacturing. However, because the primary mode of action is cellular, the assignment of jurisdiction to CDRH provides more limited consideration of the biological origins and actions of the cellular components and may require more stringent conditions for manufacturing under CGMP than for tissue processing under GTP standards.

Assuming that all cellular products are handled in Class 100 biological safety cabinets, incubated in HEPA-filtered incubators and handled by trained staff wearing protective clothing, more important to the material safety than the manufacturing environment is the composition and the origin of the reagents through which the cells

pass during processing, as we have heard from others.

[Slide]

This flow diagram summarizes the suggested jurisdictions of CBER and CDRH for combination materials for allogeneic cells. Again, acquisition can be managed under AATB standards, and the GTP procedures that are being developed will provide confidence in the process controls, and then development of release criteria and tissue tracking as already exist, again, with the matrix being cleared by CDRH.

[Slide]

In summary, combination materials of cells and polymeric matrix usually consist mostly of cells and act predominantly by cellular mechanisms either direct, as with autologous cells, or indirect, as with allogeneic cells. The contribution of the cellular components can be determined in preclinical studies that compare the combination materials to the matrix alone.

Risks associated with combination products

that are made from autologous cells should be considered no greater than minimally manipulated autologous tissue. In fact, risks are less because biologic fidelity to the natural tissue is usually greater.

For combination products with allogeneic cells, standards of the American Association of Tissue Banks and the developing good tissue practices of FDA provide adequate assurances of the tissue safety to patients, and maintain a very favorable benefit to risk ratio from most disease conditions.

[Slide]

In conclusion, if the primary mode of action of a combination of cells and matrix is cellular, then the jurisdiction should be primarily under CBER, not CDRH.

If the primary mode of action is matrix, then CDRH should have jurisdiction. The acellular matrix component should be reviewed by CDRH.

If the jurisdiction for combination materials is under CBER, then premarket approval

should require safety assurances of facilities' requirements as in tissue banking, such as registration and GTPs, but not include mandatory multicenter studies to demonstrate efficacy in comparison to the prevailing standard of care.

If autologous cells are used in the material, MAS guidance should be followed for the cellular component.

If allogeneic cells are used, then tissue banking practices should become the reference standard.

Process controls and release criteria that are specific to the material should be required to provide assurances of safety. Any additional procedures or reagents not typically used in tissue banks, such as animal cells or animal byproducts, should be reviewed for consideration of safety before marketing approval, and most frequently these will be biologic.

Finally, most combination products should not require multicenter studies as an obligatory requirement, unless the sponsor is seeking specific

product claims. Thank you for your attention.

MR. BARNETT: Thank you, Dr. Boyce. Your agenda shows an afternoon break, but what I would rather do is go on to the final speaker shown on the agenda, and then we will see if there is anyone that wants to speak from the floor or if Dr. Zuckerman has arrived. So, our final speaker is Ms. Andrea Chamblee, of BioWhittaker.

BioWhittaker

MS. CHAMBLEE: Thank you very much for having me.

[Slide]

My name is Andrea Chamblee, and I am here representing BioWhittaker, Inc. BioWhittaker makes media and sera, and as our customers have moved into the cell therapy field, we have expanded into that field with them. We have expanded our capacity as a contract manufacturer in cell therapy, and it is in that capacity that I hope to provide some information to the panel.

As you have heard the speakers say before, this is a vibrant field with lots of activity.

That has been, in large part, due to the contribution of CDRH review. We recognize CBER's important contribution but we are here to ask for consistency in review. In the event that a transition is imminent, we have some suggestions and requests to make in that regard.

I would also like to raise the issue of some activity that is going on under FDA's radar screen in hospitals that are free from FDA regulation right now, and provide some suggestions for that.

[Slide]

The important considerations that I want to address today are these: The standard for changing FDA's product jurisdiction is a public health standard. Existing safeguards and review processes that are already in place assure public health and product safety. Absent a serious safety issue that can't be addressed under the current regulatory oversight, consistency and predictability must be maintained. If public health is the basis for reassignment of the center,

careful management of that transition is necessary--
-I guess what AdvaMed called practical impediments.

[Slide]

I will address these points in the context of the questions that FDA raised. Question one regards the public health concerns related to these products.

There are no public health concerns that are outside the jurisdiction of any particular center. For a product that is cleared or approved by FDA review with intercenter consultation, that is manufactured according to GTPs which do apply to devices derived from tissue, and under the Quality System Regulation, subject to periodic inspections, the safety issues have been addressed. And, the product jurisdiction process for all products recognizes the thorough review that is available regardless of the center.

[Slide]

The second part of question one regards the information that the agency should require in a submission. Regarding the agency lead center, the

question really goes beyond the scope of a decision to change a lead center. Nevertheless, it is important for FDA to assure that products with similar indications will be subject to similar clinical requirements and similar manufacturing controls.

[Slide]

The last part of question one is regarding the regulatory requirements necessary. The Quality System Regulation for devices and good tissue practices are adequate to assure the safety of these wound healing products. Changing the requirements from the device Quality System Regulation to other systems, such as the GMP used by drugs and biologics, will really have enormous repercussions on industry. It will redirect resources to restructuring these systems that still address the same concerns. It will require an enormous amount of resources that will delay product availability and product advances that can have a real effect on safety and efficacy without adding any real value to the manufacturing

controls. By the way, the Quality System Regulations do incorporate all the concerns of the GMPs that some of the speakers talked about before.

[Slide]

Question two regards the primary mode of action. The important considerations here are that the standard for changing FDA's product jurisdiction is public health, not primary mode of action. It is worth noting that from the beginning of the product jurisdiction process companies have been encouraged to submit their requests for designation as early in the process as possible. I heard this same urging at the Drug Information Association meeting as early as last week.

Now, it is reasonable to know that there is going to be some more information about the product's mode of action after the request is granted, while the clinical information is being gathered and the decision and product jurisdiction shouldn't be jeopardized by the acquiring of this additional information.

[Slide]

The current statutory requirements reinforce this provision. It says that the Secretary can't change this decision except for public health reasons based on scientific evidence. When there is inaction of the Secretary, the decision stands unless there are public health reasons based on scientific evidence.

[Slide]

The current regulations also say that the effect of the letter of designation will stand, except to protect the public or for other compelling reasons. So, public health should be the reason to change this decision, not the primary mode of action.

[Slide]

Again, this is reinforced by the regulations on the effect of the letter of designation. And, a change in the agency component also has some procedural requirements, concurrence of the Deputy Commissioner of Operations or the Deputy Commissioner for policy.

[Slide]

There are additional procedural requirements that may apply here. I guess it is reasonable to anticipate that dispute may occur from changing some products to another center. So, these procedural requirements may be implicated in this case.

[Slide]

As far as the public health evidence to support the change, the Federal Register notice of this meeting didn't identify any particular public health or safety issue. So, I looked on MedWatch on my own to find out if there was a safety issue, and this is what I found: From years 1999 to 2002 there was one safety issue for a product called T-Seal, which may or may not fall under this but I didn't see any others, and it was adequately managed by CDRH under their current authority. That is out of 203 reports on MedWatch. So, these products seem pretty safe.

[Slide]

Also, there is a new initiative. I think it is only a week old. It appeared in the Federal

Register. So, if there are new safety issues, FDA has the authority and a procedure to identify them and track them, and require changes.

[Slide]

So, in this environment where the products seem particularly safe, we have the luxury of considering the benefits of consistency.

Consistency might be achievable even if this is moved to the Center for Biologics as a device as long as the transition is carefully executed.

[Slide]

We have some historic experience with treating new products differently, and it is not helpful. We have the human heart valves, imaging agents and Diapulse. It makes industry nervous when we talk about a change based on these past experiences. Perhaps there are others that went more smoothly but they don't get the press that these do. So, a transfer needs to conserve agency resources and facilitate product availability. The agency needs to take a hard look at procedures in place to make sure any change is done smoothly.

[Slide]

The transitional issues that we would like to address will, hopefully, conserve FDA review resources. We seek consistency of reviewers in the event of a transition so that the same people who have grown up with the agency in this field will remain with their products. The review standards should be the same. The inspection standards and schedules should remain the same and, in particular, the manufacturing requirements that I spoke of under the QSR. If product availability takes the dip that we might have experienced, say, in the past with human heart valves, it is hard to argue that there will be a public health benefit from transferring, but, in sum, if the transfer is handled well there may be a public health benefit.

[Slide]

On the other hand, requiring a different kind of application, it can't really be argued that it would conserve agency resources. The application for the premarket approval contains an exhaustive amount of information that we heard

about already today, and it contains adequate information already to protect the public health. Changing from a different application, like a BLA or to a different system of GMP, would replicate expertise and not conserve resources with FDA or with the industry.

Reducing delays from consults may conserve agency resources, but we are concerned about the discussion that we hear about collaborative review where perhaps no center will own the review and the deadlines might be uncertain, and that won't conserve FDA resources. So, we seek that any transition will address any potential delays from consults or collaborations.

[Slide]

So, our conclusion to question one is that the current safety oversight is already exhaustive. There is no contention generally, we have heard, that the safety review for devices is less adequate than that for biologics, and no evidence that safety has been or will be sacrificed. And, there is no contention that any special safety issues

exist for these products. So, in that light, any transition must be managed very carefully. We also urge that it occur quickly to avoid the uncertainty that has been experienced in the industry over the past several months.

[Slide]

Question three regards how to evaluate the primary mode of action in combination products.

[Slide]

Again, the standard for changing FDA's product jurisdiction is public health, and we have made that point already.

[Slide]

In the event of a transfer, it would be reasonable to consider where the expertise already exists so that we can facilitate review and product availability, and conserve agency resources. It would also be reasonable to consider the likely direction of the technology to prevent the need for future duplication of expertise.

[Slide]

Again, the current review procedures are

already exhaustive. There is no contention that review now is inadequate, and no evidence that review issues have gone unaddressed for any of these products.

[Slide]

Next, I want to talk about the other considerations, the practical implications that AdvaMed mentioned. Delays have already been experienced in our industry over the past, like in any new technology but in particular over the past few months. It affects the ability to prepare submissions. It jeopardizes or at least calls into question the agreements with CDRH on clinical requirements. We suspect that it contributes to agency consult delays and inconsistent review standards that might also be occurring. Some of these complexities aren't related to FDA; some are. But they all implicate product availability, and that is a safety issue that we challenge FDA to address.

Also, I would like to raise the point that most of the activity in this field is already

occurring in hospitals outside of the scope of FDA review, and FDA resources might be better spent corralling these outliers rather than putting resources into moving the product from one center to another.

[Slide]

There also has been some confusion that I have heard in the audience about whether these products are going to go to CBER as a device or as a biological product, and we haven't heard too much comment on that because I think there is some confusion and the Federal Register notice doesn't tell us whether these are likely to be biologics with a license or a device. So, this meeting won't provide too much comment on that, I am afraid.

[Slide]

This undermines the very purpose of product jurisdiction which is certainty. It undermines company decisions to proceed on products that are in the pipeline that must be made every day. For cell processors, people who engage in cell processing and people who need to establish

good systems for their cell processing, it undermines the company decisions regarding their GMP systems. We don't know what is going to happen to the enormous investments we make in QSR if it is going to be switched to good manufacturing practices.

MR. BARNETT: Two more minutes.

MS. CHAMBLEE: Thank you.

[Slide]

I am at my summary slide, and that is that the standard for changing FDA's product jurisdiction is public health. The existing safeguards and review processes are adequate to assure the public health and product safety. Absent a serious safety issue that can't be addressed by CDRH, consistency and predictability should be paramount. If public health is the basis for this reassignment, careful management of the transition is necessary.

I would like to draw an analogy for this industry. It is like a young person on the brink of adolescence being asked to choose which parent

they want to live with. We don't want to make that decision.

MR. BARNETT: Who is mom and who is pop down here? Let's not go there!

[Laughter]

MS. CHAMBLEE: What we need is some levity at the end of the day. But it is an uncomfortable question. It is disrupting question. You can't expect a child to go back and pay attention to their homework after you raise a question like that. And, like that young person, the industry needs and deserves consistency. So, I make the request for that of the agency. Thank you for your time.

MR. BARNETT: Thank you, Ms. Chamblee. Are there any questions from the panel?

DR. FEIGAL: Just a quick one, Mark.

MR. BARNETT: Yes.

DR. FEIGAL: Could you elaborate a little more on the practices in the hospitals that concern you?

MS. CHAMBLEE: No. Well, our experience

is people come to us for advice and they have already begun some of their work. Our contribution is to introduce some additional requirements that should be imposed on the next phase of that work. And, we see some work done in hospitals and laboratories that run the gamut to GLP to borderline QSRs. We just see people at all phases of sophistication and all phases of research engaged in this activity in their hospital laboratories or in their academic research centers, and we can help them improve their processes to be ready for an application but a lot of these people are operating under the FDA radar screen. They don't seek additional expertise, and they continue the way they are. We think that raises safety issues for the patients involved, and it raises the same cross-contamination issues that we talked about that can be addressed under the GTPs, that we think are the right thing to do whether you are a biologic or a device.

DR. ZOON: Just one quick clarification just so the audience understands, the GTPs is a

proposed rule; it is not a final rule. So, it is not actively in place right now, and we have received a number of comments on that and we are addressing the comments. But I just wanted to be clear that the GTP is not a final rule; it is a proposed rule.

MS. CHAMBLEE: That is true. Our experience though is for an applicant who doesn't follow GTPs, they raise safety issues that will cause their applications to be on hold, and rightfully so. Contamination and cross-contamination are serious issues.

DR. ZOON: We agree.

MR. BARNETT: Any other questions? Thank you very much.

MS. CHAMBLEE: Thank you.

MR. BARNETT: First of all, has Dr. Zuckerman arrived? Someone else will give Dr. Zuckerman's presentation, and it is coming off the fax machine right now. I don't think we need a break. We will move ahead.

Let me also ask the other question, and

that is does anyone here want to speak from the floor who had not registered to speak? I don't see any hands on that. So, while we wait for the fax machine to warm up, let me ask Suzanne O'Shea to give some final comments on behalf of the Ombudsman's Office. Can you do that?

MS. O'SHEA: Our final comments are just to thank everyone for coming on behalf of the panel and the agency. We appreciate all your comments. We certainly will take them under careful consideration.

We wanted to remind everyone that the docket is open until August 23rd. So, please submit your comments if you have any additional comment to make. We would appreciate that. And, thanks again for coming.

MR. BARNETT: Thank you. Let's wait for a few minutes and if it doesn't show up we will adjourn. Yes, sir? Give your name and affiliation.

Open Microphone

MR. HOGAN: Jim Hogan. I am the chief

operating officer for Modex Therapeutics. Modex is a Swiss-based biotechnology company with a number of different FDA applications in process right now. So, it is a meeting of great importance to us, and I thank you very much for giving the opportunity for people to make their say. It was a very interesting meeting.

I have a question actually and maybe a comment or two so maybe I will make the comment and then pose the question. There was near unanimity of opinion from the speakers today that there was no great immediate public health concern that was necessitating a change in jurisdiction. I think that was reflected in sort of an overall theme as I listened to these comments, that overall theme being that if the situation isn't broken right now, let's not break it with some sort of a change.

I guess I share that sentiment from the standpoint that if the system is working I am concerned about the system changing, such that the transparency, the predictability of it changes; maybe the expense of it changes; all those sorts of

things because especially for the smaller companies, like ours, that is of great concern to us--the ability to predict, and to predict to our investors what is going to happen. So, I am glad for the opportunity for people to be able to make that opinion known and I would just like to add to that opinion.

I guess the question that I have then, if it is okay to ask a question. Perhaps this is mostly to Dr. Zoon but perhaps anybody from the panel could comment on it. There are a couple of different outcomes that could come from here. One outcome could be that no changes are made; that these products continue to stay with the device section and then there is nothing to do. Another option could be though that they get shifted over to CBER. If they get shifted over to CBER, then the big question that again comes up is are these products that were devices in the past going to start to be biologics, or are they going to become NDAs or something else?

I guess my question is one of procedure.

If the decision ultimately is made to move them over into the CBER jurisdiction, what is the process that the agency will likely go through to incorporate industry into those decisions at that point to determine what is going to be a device; what is going to be a biologic; what is going to be what so that some of these concerns of industry don't bubble up to become reality?

DR. ZOON: Well, as you know, today we are here mostly to listen and to hear the opinions. I think in some ways it is unfortunate that the discussion with respect to BLA and PMA really was less targeted today. It seemed to be more targeted to which center rather than jurisdictional mechanism, although I think you could interpret the information in many ways.

So, I think based on the discussions following this meeting and what other information we get in, the Center for Biologics, as I mentioned earlier, has many pathways that we can choose depending on these products. I think the reality in such a transition is looking at consistency,

smoothness of transition and fairness for all these products. So, if a decision is made to go forward I am sure it will be one of many continuing discussions and not just a one time interaction through this particular meeting.

My own sense is that these issues, from banked human tissues through complex cellular products, still will need to be based on a matrix type analysis, and to the level that the agency can draw some clear lines, I think that will help the industry. We will look at the supporting data for the proper mechanism for these products and, if they were to come to CBER, how best to manage these products. I think we can look at several mechanisms. Again, whether or not they are under the tissue framework with the GTP donor eligibility or 510(k) PMA and BLA process, I think are all legitimate. So, to the level that we can get more feedback to the docket on this, I think that will be helpful. Thank you.

MR. BARNETT: Anyone else? If not, Dr. Lee will be speaking now for Dr. Zuckerman. Is

that correct?

**National Center for Policy Research for
Women and Families**

DR. LEE: That is correct. I would like to apologize to everyone here. Like many people who work in Washington, Diana Zuckerman tries to be in two places at once and today she didn't quite make it.

This is the statement of Diana Zuckerman, president of the National Center for Policy Research for Women and Families.

Every year, a large number of patients require artificial skin products to aid their recovery, including patients suffering from burns, diabetic cutaneous lesions and traumatic injuries. The safety and effectiveness of these products are tremendously important to patients and their families. We look to the FDA to ensure that the interests of these vulnerable patients and their worried families will be paramount, as the agency determines the optimal manner in which to regulate these products.

We strongly believe that regulatory jurisdiction for combination products should be determined on a scientific basis, not on historical precedent. The most important questions are:

One, what is the optimal approach for determining the primary mode of action of these combination products?

Two, What is needed for the FDA to assure the safety and efficacy of these combination products in terms of premarket review, postmarket surveillance and inspections?

In assigning jurisdiction over the regulatory process for wound healing combination products, primary must be given to the specific characteristics of each product under consideration, rather than historical precedent. A center should not be awarded jurisdiction over a combination product simply on the basis of its psychotic jurisdiction over earlier products in the same category. The products being discussed today have advanced far beyond the simple wound coverings of yesteryear, and will continue to grow in

complexity.

The complexity of these products are, with few exceptions, primarily attributable to their biologic component. For example, the complexity of Integra resides primarily in its lower layer, which is composed of interwoven bovine collagen and carbohydrates. The porosity and biodegradation properties of this lower layer are crucial to the proper functioning of the product. In contrast, the upper layer consists of a relatively simple silicone sheet that is removed after a period of healing.

Future products may incorporate growth factors, cytokines, angiogenic agents, and even genetically modified cells. Living cells are already key components in some wound healing products, for example Epicel, which utilizes cultured human keratinocytes and are likely to play an even greater therapeutic role in the future. With the increased use of biologic components comes an increased need for vigilance against potential complications, for example, infection, inadequately

controlled cellular growth and rejection, that may arise from biologic products.

We believe that the primary mode of action should determine jurisdiction for combination products. The pertinent issue is how the FDA should evaluate the components of a combination product to determine its primary mode of action. For any combination product, jurisdiction should be based on an objective evaluation of every new product.

Most wound-healing combination products rely primarily on their biologic components for therapeutic effect. There is a distinct trend in the field away from producing relatively simple wound coverings that act as temporary physical barriers and towards permanent, biologically interactive products that actually promote healing and regeneration. With those factors in mind, an objective evaluation of each new combination product should include the following criteria:

One, which component of a combination product is most interactive with the human host?

If we take the example of Integra, its unique properties rest almost entirely in its lower, biologic layer. Composed of a matrix of interwoven bovine collagen and glycosaminoglycan carbohydrate molecules, the lower layer is designed to coax the host's surviving fibroblasts and other supporting cells into regenerating a dermal layer of skin.

Two, which component is most complex in design and structure?

Again, taking the example of Integra, the upper silicone layer is not nearly as complex in structure and design as the biologic lower layer which incorporates complex protein and carbohydrate molecules. Needless to say, living cells and tissues are far more complex in design and structure than any inorganic component.

Three, which component require a more complex production and manufacturing process?

A more complex production and manufacturing process makes it more difficult to maintain quality assurance standards. As an example, one can turn to the difficulty in culturing

living cells. Even small changes in procedures related to nutritional media, antigen quantity, incubation temperature, and infection control may seriously affect the safety, efficacy, viability and stability of cultured cells. Another example is the precise production controls needed to regulate the porosity and biodegradation properties of Integra's lower biologic layer. It seems likely that in nearly all cases, regulating the production and manufacture of biologic components will pose a more serious challenge than regulating the production of non-biologic components.

Four, which component has the most potential for producing serious complications?

The increased incorporation of biologic components in medical products poses the threat of introducing new and serious complications seldom seen in the past. For instance, the use of living cells could result in the introduction of viral contaminants. Some future products incorporating living cells may need to be carefully monitored for adequate cellular growth and reproduction control.

The antigenicity of biologic components needs to be carefully tested and controlled to prevent rejection and the induction of autoimmune disorders.

In light of the important role of biologic components in wound healing combination products, it seems reasonable that in most cases the FDA should assign jurisdiction to the center best suited for evaluating biologic products. Ideally, such an agency would have in-house expertise in molecular cell biology, infectious disease, immunology, genetics, and embryology. Such expertise will also be invaluable in addressing concerns regarding perceived threats like bovine spongiform encephalopathy.

As noted earlier, the increased complexity of future wound healing combination products will almost certainly be attributable to their biologic components. Jurisdiction should be assigned to the center that is most capable of addressing the four criteria mentioned above.

Finally, the center assigned jurisdiction

over these combination products should be provided adequate regulatory authority and sufficient resources to ensure the safety and efficacy of these products. The designated center should have a demonstrated commitment to well-designed postmarket surveillance studies, as well as the authority to require such studies and to impose civil monetary penalties and other sanctions against manufacturers who fail to complete such studies.

I should not that the CBER does not have the authority to impose civil monetary penalties, but we believe that such authority should be granted.

Sufficient resources must be provided, preferably through appropriations, that allow the hiring and retention of personnel with expertise in relevant fields in biology and medicine. Resources must be provided to ensure adequate staffing for facility inspections and adverse event monitoring. We have strong concern that any centers that are having difficulty in meeting the staffing

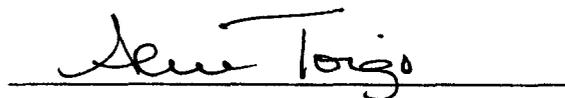
requirements for inspections and adverse event monitoring should not be given the additional burden of regulating these complex combination products. Thank you.

MR. BARNETT: Thank you, Dr. Lee. If there are no further questions from the panel, I think we could call this meeting adjourned. Thank you very much for coming and have a safe trip home.

[Whereupon, a 2:30 p.m., the proceedings were adjourned]

C E R T I F I C A T E

I, ALICE TOIGO, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

A handwritten signature in cursive script, reading "Alice Toigo", is written above a solid horizontal line.

ALICE TOIGO