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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

Open Public Meeting

Human Bone Allograft: Manipulation and Homologous Use in Spine and Other Orthopedic Reconstruction and Repair

Wednesday, August 2, 2000

8:30 a.m.

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PARTICIPANTS

Session 1 - Kathryn C. Zoon, Ph.D., Moderator

Panel Members:
Kathryn C. Zoon, Ph.D.
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Ruth Solomon, M.D.
Antonio Pereira. M.D.
Martha A. Wells, MPH
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Session 4 - Philip Noguchi, M.D., Moderator

Panel Members:

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C O N T E N T S

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SESSION III - Public Discussion/Comments

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C O N T E N T S (Continued)

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P R O C E E D I N G S

DR. ZOON: Welcome to the Open Public Meeting on Human Bone Allografts. I just want to, one, thank everybody for attending this important open public meeting, especially on such short notice, as well as to also thank you for coming to Washington in the summer. That is very brave and we appreciate it.

I am Kathryn Zoon. I am the Director at the Center for Biologics. This workshop is co-hosted by the Center for Biologics and the Center for Devices and Rad Health, and Dr. David Feigal, the Center Director for CDRH, is here, as well, and will be speaking in a few moments.

This is an important meeting to the FDA because we are in the process of finalizing our proposed regulations on human cellular and tissue-based products, and to potentially develop guidance to assist with some of the more technical aspects in applying the definition of minimal manipulation and homologous uses as they relate to bone allografts. We certainly need the input from all of you to make sure that we do the very best job we can in providing guidance to the affected parties.

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We have requested information from all our stakeholders today specifically on five questions that are listed on the overhead. I will just briefly review those.

The first is which processing procedures applied to human bone allograft fall within or outside of FDA's proposed definition of minimal manipulation.

The second, which uses of human bone allograft fall within or outside FDA's proposed definition for homologous use.

What risks to health have been identified and characterized for human bone allograft products.

What control have been identified to adequately address the risks to health of use of human bone allograft products.

What industry standards for bone allograft products are available, and what standards will be needed in the future.

FDA is here today to listen to you in order to understand how you see bone products fitting into the regulatory approach we have proposed. We are hoping to hear specific data and information which will assist us

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with this task.

We have not asked today for reiteration of comments that have already been sent to the docket on the two proposed regulations to date. We are currently addressing these in the final regulations for establishment, registration, and product listing and for donor suitability.

Also, FDA is not here today to make decisions, draw conclusion, or answer specific questions on issues presented today. We are here today to listen and ask questions of you to help clarify where to draw the line between minimal manipulation and more than minimal manipulation and between homologous use and non-homologous use specifically for bone allografts.

A summary of the meeting will be prepared and be available on our web site, along with the transcript of this meeting. Additional comments can be submitted to the docket through September 1st. We are looking forward to hearing from you and then hopefully, this information that you present today will be important in the future of our guidances and regs.

Dr. Feigal is going to join us. David, we are

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happy that we could do this together with CDRH and we really appreciate the joint cooperation and efforts in putting this together.

David.

DR. FEIGAL: Good morning. We have an ambitious schedule to get through today, so I am not going to make very long remarks.

When I think about this area, I often remember an anecdote, and I apologize. I have used this before, so you may have heard it. But when I was a student, the chairman of surgery was Robert Chase, who is a very noted hand surgeon. In presenting cases to him, there was a case presented from a medical school about 35 miles away where a fire-fighter had lost his thumb. The standard operation at that time would have been to swing the index finger over and put the index finger in the thumb position and then you have a three-fingered hand and a very long thumb, and it's a quite functional hand.

But what they had done at the other medical school was that they had transplanted, they had moved up the toe, the great toe from the foot of this fire-fighter up and used microsurgery techniques which were just

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beginning to flourish at that time, the first use of microscopes for suturing of small structures, and they had actually successfully moved his toe up to this hand.

So, that made a very ugly thumb. Dr. Chase was asked to comment on this, and in part because the toe actually has a lot to do with your balance, and fire-fighters need to be quite mobile, and not being a man of very many words, his comment to sum up the case before he moved down to the next one was that, well, this sounded like a triumph of technique over reason.

I think as we look at some of the things that are new, some of the things that are on the forefront, one of the challenges for us is to find that boundary where we don't want to have a triumph of regulation over reason, we recognize that these areas where there are long-standing uses, long-standing practices, that we need to find a way to blend the regulatory scheme into the current practices, but also identify the new challenges that are going to come along as techniques change, as new things become possible, and we are all aware that we are seeing an increasing growth in the whole area of hybrid types of products that present multiple challenges.

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So, we are here to listen. We welcome very much your helping us with this area, and I look forward to your comments.

Thanks very much.

SESSION I - BACKGROUND INFORMATION

Moderator: Kathryn C. Zoon, Ph.D.

Overview of the Proposed Approach to the Regulation of Human Cells and Tissues

DR. SOLOMON: Good morning. I am Ruth Solomon. I am the Director of the Human Tissue Program in CBER. I want to thank all of you for coming here today to help us tackle this challenging topic.

I am going to be talking about the proposed approach to the regulation of cellular and tissue-based products which FDA published on February 28th, 1997. The purpose of the proposed approach was to develop a comprehensive approach to a wide spectrum of cell and tissue products to protect the public health, but at the same time to permit innovations without unnecessary regulatory burdens. Therefore, the approach that we came up with is a tiered, risk-based approach with products having the least risk being the least regulated.

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This umbrella approach included cells and tissues that were already regulated by FDA, such as musculoskeletal tissue, skin, and ocular tissue, which were regulated since 1993 under 21 CFR 1270. Dr. Pereira will be telling you more about this current regulation.

Also included were some products that are currently regulated as medical devices, namely, human heart valves and dura mater. In addition, under this umbrella we propose to include somatic cell and gene therapy products, manipulated bone marrow stem cells. These are currently regulated as licensed biologic products.

In addition, the umbrella would include combination products which are already regulated under 21 CFR Part 3.

The umbrella approach would also include some cells and tissues not currently FDA regulated, namely, hematopoietic stem cells from peripheral blood and cord blood and reproductive cells and tissue.

The umbrella approach did not include vascular human organs because these are regulated by a different federal agency, namely HRSA. They did not include whole

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blood, blood components, and blood derivatives, because they have their own well worked-out regulatory mechanism.

It would not include secreted or extracted products. It would not include minimally manipulated bone marrow, which is also regulated currently by HRSA. It would not include ancillary products used in the manufacture of cells and tissues, and cells, tissues, and organs from animals. These two last things have their own regulatory framework being developed. It would also not include in vitro diagnostic products.

When we worked to develop the proposed approach, we discussed five concerns that FDA had regarding the regulation of these products. They included transmission of communicable disease, processing controls to prevent contamination and preserve product integrity and function, clinical safety and efficacy, promotional claims and labeling, and how we could best monitor and educate the industry.

Taking each concern and briefly showing you how the approach is a tiered, risk-based approach, the first being transmission of communicable disease, we propose that if cells or tissues were used during a single

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surgical procedure, that is, they were not banked with other cells and tissues, there would be no requirement under this umbrella approach.

For autologous and reproductive cells and tissues from sexually intimate partners, we would recommend certain donor testing and screening procedures, and for all others, cells and tissues from allogeneic donors, we would require donor testing and screening.

The second concern was having control over processing. Again, the tiered approach proposed that for cells and tissues used in a single surgical procedure, there would be no requirement under this framework. If a product was regulated solely under Section 361 of the Public Health Service Act -- and I will have more to say about that a little bit later -- this is the section of the Public Health Service Act which allows us to promulgate regulations to prevent the transmission and spread of communicable diseases.

If a product was regulated solely under Section 361, then, we were planning to propose good tissue practices for such products and the good tissue practices would be aimed at preventing contamination and preserving

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the integrity and function of the product.

If the product was more highly regulated under the FD&C Act and/or Section 351, which is the licensing procedures of the PHS Act, these products would have to follow GTP and the good manufacturing practice or quality systems currently in effect for these products.

For clinical safety and efficacy, again, if a product was regulated at the lower end of the spectrum, that is under Section 361 of the Public Health Service Act, there would be no submission to FDA, that is, no premarket approval would be required.

However, if the product was regulated under the FD&C Act and/or the licensing provisions of the PHS Act, then, a submission to FDA would be required, and that could take the form of an IND or an IDE, if the studies were investigational or a BLA or PMA or 510(k).

Of course, the submission would have to receive approval before the product could go on the market.

Next, we were concerned about promotion and labeling of a product, so again for products used in a single surgical procedure, that is, not banked, there would be no requirement. Products regulated solely under

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361, FDA would not have to review the labeling, but we would assume that the labeling was clear, accurate, balanced, and non-misleading, and this would be determined at the time of inspection.

If the product were regulated under the FD&C Act and/or the licensing provisions of the PHS Act, then, labeling would be submitted to FDA along with the application.

In order to implement, the proposed approach, we envisioned setting forth three proposed rules, two of which have already published - the establishment, registration, and listing proposed rule, published on May 14th, 1998, and the second proposed rule, suitability determination for donors of human cellular and tissue-based products published on September 30th, 1999.

The docket for the second proposed rule was reopened and recently closed again on July 17th.

The third proposed rule, current good tissue practice, which would also include inspection and enforcement provisions, has not yet published, but we are working on it.

Just briefly to review the contents of these

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proposed rules, the establishment, registration, and listing contained a purpose and scope, contained certain definitions, set forth which establishments would be regulated solely under Section 361.

It didn't at that time, but subsequently in the donor suitability reg, we also developed criteria for regulation under the FD&C Act and/or Section 351 of the Public Health Service Act, and also it describes establishments not required to comply with the requirements.

In the Definition Section, there are three definitions that are particularly important for today's discussion.

The first is the definition of the human cellular or tissue-based product, which is the product containing or consisting of human cells or tissues intended for implantation, transplantation, infusion, or transfer into a human recipient. Previously, I discussed which cells and tissues would not fit under this definition.

Another important definition that is going to be helpful to us today is the definition of what we mean by

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homologous use. It is use for replacement or supplementation and for structural tissue-based products which are the ones we are going to be discussing today, bone allograft, homologous use occurs when the tissue is used for the same basic function that it fulfills in its native state, in a location where such structural function normally occurs.

We also had a second part of the definition for cellular and non-structural tissue-based products which is not pertinent for today's products that we are discussing.

The next definition that we will want to explore is the one for minimal manipulation. Again, for structural tissue which we will be discussing today, minimal manipulation means processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement.

Again, there is a second part of the definition for cells and non-structural tissue.

The establishment registration proposed rule set out the criteria for regulation solely under Section 361

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of the Public Health Service Act. That is, these products would not require premarket approval or a submission to FDA, but would have to adhere to donor suitability and testing and the good tissue practices.

The criteria that would allow a product to fit under this category are that the product is minimally manipulated, is not promoted or labeled for any use other than a homologous use, is not combined with, or modified by, the addition of any component that is a drug or a device, and either does not have a systemic effect or has a systemic effect and is for autologous family-related allogeneic or reproductive use.

Please note that a product must meet all four criteria in order to come under this category of regulations solely under Section 361.

We then described products that would be more highly regulated, that is, they would come under the regulation under the FD&C Act and/or Section 351 of the Public Health Service Act.

Such products, again to reiterate, would require a premarket review and approval by FDA for clinical safety and efficacy.

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In order a product to be regulated under this category, any of these criteria would apply. It is more than minimally manipulated or it is promoted or labeled for any use other than a homologous use, or it is combined with or modified by the addition of any component that is a drug or device, or it has a systemic effect and is not for autologous, family related, allogeneic or reproductive use.

Then, I thought I would briefly go over the contents of the rest of the establishment registration regulation and also the donor suitability and broadly for the current good tissue practice proposed reg, which has not yet published just to complete the picture, but these points that I am making are again background, and are not really key to what we are discussing today.

So, in addition to what I have already mentioned, under the establishment registration, there are procedures for when to register and list, how and where to register and list the information that you are required to submit on the form, then, a discussion of amendments to your registration, assignment of a registration number, and inspection of the registration

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and product list by other others.

The donor suitability proposed rule, which published in September 1999, contains the following points. There is what do we mean by determination of donor suitability, what records do you have to keep about donor suitability including records that have to accompany the product, quarantine requirements until donor suitability is determined, the disposition of a product from a donor determined to be unsuitable, and there are certain situations where FDA would not prohibit the use of a product from an unsuitable donor provided that certain controls were in place.

It discusses in detail donor screening for particular relevant communicable diseases, donor testing for particular relevant communicable diseases, and certain exceptions where the donor screening and testing are only recommended, but not require, but there need to be certain labeling controls in place.

The current good tissue practice proposed rule, which we will publish shortly, will contain a general discussion of what do we mean by good tissue practice. There will be a section on exemptions and alternatives.

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The focus will be on having a quality program and control upfront. There will be discussion of organization and personnel, procedures, facilities, environmental control, equipment, supplies and reagents, process controls, changes in validation, labeling controls, storage receipt and distribution, records, tracking of the product, and complaint file.

In this last proposed rule, there will also be additional requirements for reporting, labeling, and claims, and there will be regulations that cover inspections, imports, and enforcement activity, such as orders.

Lastly, I would like to say a few words about the Tissue Reference Group, also known as the TRG. The TRG was established and actually had its first meeting in March of 1997. It grew out of the proposed approach where the concept of having a Tissue Reference Group was first introduced.

The group consists of representatives from both centers, from CBER and CDRH, and also there is a representative from the ombudsman's office and an executive secretary.

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The purpose of the TRG is to provide a single reference point for product-specific questions involving jurisdiction, policy, or regulation. The TRG does not make decisions per se, but rather makes recommendations to the two centers who then consider the recommendations and decide how to proceed.

The TRG can also make recommendations to the ombudsman's office. That is the Office of the Chief Mediator and Ombudsman. Some of the information that the TRG reviews consists of proprietary information that would not be available to the public. However, if the decision affects a class of products, we are committed, as explained in the proposed approach, to put forth a guidance document or a revision of existing regulations if that seems appropriate.

The TRG has an SOP and annually updates the types of decisions it has made, and these are available on the CBER external web site.

So, basically, I have given you an overview of how we are proposing to regulate human cellular and tissue-based products and now Dr. Antonio Pereira from the Human Tissue Program will discuss what the current

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regulation consists of.

Overview of the History of FDA Regulation of Bone As a Tissue

DR. PEREIRA: Good morning. I am Antonio Pereira. I am a practicing otolaryngologist, head and neck surgeon, and also a medical officer at the Human Tissue Program.

I would like to give you some historical background of all the regulations that stand now and where all the regulations that were proposed come from.

The first date is 1902, 100 years ago almost. The Biologics Control Act that requires the purity and safety of serums, vaccines, and similar products.

Then, in 1944, the Public Health Service Act defined on Section 351 a biological product as any virus, therapeutic serum, toxin, antitoxin or an analogous product applicable to the prevention, treatment, or cure of diseases or injuries of man.

On Section 361, it allows for regulations necessary to prevent introduction, transmission or spread o communicable diseases.

It goes further in 1972, regulations of

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biologics is transferred from the NIH to the FDA, and in 1987, the Center of Biologics, Evaluation, and Research was created after a reorganization of CDER, the Center for Drug Evaluation and Research.

So, CBER started to look on human tissue regulation in the 1990s. There were reports to the CDC about transmission of HIV through fresh frozen bone transplant, and in 1991, there was a Public Health Work Group recommended, federal development and publication of standards or guidance under screening and testing, and tracking procedures to prevent the transmission of infectious disease.

Further on in 1993, there were reports of importation of human tissue that was not properly screened and tested for HIV and hepatitis, and there was a Senate hearing on appropriate oversight on human tissue banking. This was just a Committee on Regulation, Business Opportunities, and Technology, a Committee of Small Business. That was on October 15 of 1993.

Both the workshop and the Senate gave some recommendations. First of all, persons involved in human tissue banking advocated that legislation setting forth

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regulatory requirements for human tissue banking be passed, and the Public Health Work Group recommended federal agencies proceed as expeditiously as possible to reduce the risks of transmission of infectious disease by human tissue transplantation.

Then, on December 14, 1993, an interim rule was published and was effective immediately. This rule requires screening and testing for HIV, hepatitis B and C, of all human tissue intended for transplantation, and it was published under the authority of Section 361 for the prevention of the spread of communicable disease.

This interim rule included conventional banked tissue. This is like skin and bone, things were banked on different tissue banks, excluded vascularized organs, human male reproductive tissue, and bone marrow, and excluded products regulated as drugs, biological, medical devices. It was more focused on the prevention of the transmission of disease.

The language that was published in the entry rule, in the preamble, just stated that tissues that are processed or stored, only ways to prevent transmission of infectious disease and to preserve clinical usefulness

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will be covered by the regulation.

Tissues whose structural function or functional characteristics that has not been changed through processing or other techniques will be covered by the regulation.

This rule was finalized on July 29, 1997, after review of comments submitted to the docket in public meetings and workshops. The final rule defined human tissue as any tissue derived from a human body that is intended for transplantation to another human for the diagnosis, cure, mitigation, treatment, or prevention of disease, and is recovered, processed, or stored or distributed by methods that do not change tissue function or characteristics.

So, as of today, the bone allograft fall within the scope of the final rule in human tissue intended for transplantation provided that they are not processed by methods that change tissue function, are not regulated as drugs, biologics, or devices, and are not combinations of bone allograft with other products regulated as drug, biologics, or devices.

After 1997, 1993, all this time we have been

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aware that technology advances, there are new things that come in, so that, as Dr. Solomon stated, was the proposed approach that was a tiered approach based on public health risk, is a proposed approach still.

The degree of manipulation and homologous use will determine the degree of regulation needed to assure safety and efficacy of human bone and allograft products.

As I said, this proposal will assure our public health concern, and this meeting will give you some feedback in comments from the industry. We are looking forward to a great discussion and to hear from you.

Thank you very much.

Now, you will hear the history from CDRH.

Overview of the History of FDA Regulation of Bone As a Device

MR. KAISER: Good morning. I am Aric Kaiser, the current team leader for spinal and osteosynthesis devices and a reviewer in the Orthopedic Devices Branch in CDRH, and what I would like to do is briefly go over the history of devices that we have seen in the regulation of devices that have bone as a component.

Unlike what Antonio just mentioned, where the

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biologics regulation started almost a hundred years ago, CDRH got into the business relatively recently. Devices officially, from a regulatory standpoint, didn't exist until May 28th, 1976, with the Medical Device Amendments to the Food, Drug, and Cosmetic Act.

With those amendments came along the definition of a device which didn't exist. As you can see, this is part of a big, long regulatory definition, but the important section is towards the end, where the aspect that would differentiate a device from a biologic or a drug product is that these types of products don't achieve their intended purposes through chemical action, and they are not dependent on their use as far as being metabolized.

In CDRH, there are three groups that generally tend to see these products. One is the Dental Devices Branch, and the other two are the Orthopedic Devices Branch and the Restorative Devices Branch.

From the dental point of view, there has been generally two types of bone products that they typically see, the freeze-dried bones in various shapes and sizes, and also freeze-dried demineralized bone. These products

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tend to be used for filling defects and for reconstruction.

As far as what they have seen from a regulatory standpoint, certain of these products have been viewed as pre-amendments with a recommendation that they be reclassified to either Class II or Class III depending on what the actual indication for use is.

An example of one of these products is the bio called TBM Sponge, which is a freeze-dried bone in a collagen sponge used to fill periodontal defects.

In the orthopedic and neurosurgery realm, we see similar products to what the dental group sees with the addition of the fresh-frozen bone. Again, these products are used for filling defects and for reconstructions.

What we tend to see compared to the dental group is that for the most part, the products that we would see in orthopedics and in the restorative group are post-amendments Class III devices meaning that they weren't on the market prior to May 28th, 1976. There are very new things. Examples would be the Norian SRS and the Interpore Pro Osteon 500.

We also have recognized relatively recently that

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calcium sulphate is a pre-amendments device, the example of this being the Osteoset pellets.

Some of you may remember that last summer there was a proposal and then a cancellation of a panel meeting to discuss a topic related to what we are here to talk about today, and in the information that we had released prior to the cancellation of that meeting, we were trying to get a handle on the spectrum of bone products and where things fell.

On the one end we were viewing certain bone products as being nothing but tissue. On the other end of the spectrum, you could view bone products as being devices, and at somewhere in the middle, very undefined zone, were things that had to be determined whether they were devices of whether they were tissues, and this would be dependent on how they were processed potentially, how they were used.

The other thing that I want to bring up here is that from the orthopedic standpoint, the way that we have seen some products recently, is that you can make a product from bone that's very similar to a product that we traditionally see made out of a metal or a ceramic or

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a polymer, and the fact that it is made out of bone is nothing more than a material change from the original device.

An example of that is the Bonutti Research Multitak. This is a soft tissue anchor made from allograft cortical bone and except for the fact that it is made from bone, it's identical to their previous products that are made from metal or polymer, and so the decision was made that this was simply a material change and not a new entity that we needed to deal with in the realm of the things we are talking about today.

Next, Martie Wells will come up and give you some background on the dockets and the comments for the proposals that have been published.

Overview of Relevant Comments to the Proposed Rules

Dockets Concerning Regulation of Bone Products

MS. WELLS: Good morning. I am Martie Wells from CBER. I have been acting as Project Manager for what we call the Tissue Action Plan for the last few years, which helps coordinate all of the initiatives that we have been talking about today, as well as a couple others concerning some guidance documents that we have

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been working on.

My job today is to give you a brief overview and some general categories of the comments that we have received to the docket of the two proposed rules which Ruth has discussed for establishment registration and donor suitability.

We are addressing comments to the docket having to do with these definitions and some of the other kick-up factors and will be addressing them in response to the comments within the establishment registration rule which we are currently in the process of finalizing.

Some of the general comments that we have received concerning homologous use and minimal manipulation include comments, such as the terms are vague, they are subject to broad interpretation. Other comments say they do not reflect clinical use of the products.

There were questions on how the criteria for these definitions would be applied as to what would be, as we commonly say these days, "kicked-up" to 351 or remain under 361 products for tissues.

Other comments were very explicit and said that

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these definitions should be eliminated. Others agreed that the focus that we tried to explain for homologous use is that the focus will be on promotion and labeling rather than the intent of the practitioner.

We also received requests for more guidance on how the definition will be applied, and that is one of the reasons we are here today.

Other comments -- and again I am pulling together the comments we received to both dockets in a more general fashion, and not trying to quantify them -- we received many comments concerning bone in general, especially to the donor suitability regulation. Some of these supported and some were against regulation of allograft bone. Others were either against further regulation or additional regulation concerning these products.

Many of these didn't really specify as to what they considered additional regulation as to whether they were discussing the possibilities of RGPTs or they were really referring to what was being proposed in the donor suitability regulation.

Others claimed that publication and finalization

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of these regulations was interference with patient care. It would interfere with the doctor-patient relationship and with the practice of medicine.

Many others were either in support or let's say many of them were against regulation of bone allograft as medical devices.

It was very difficult. There were many comments to the docket, many repetitive comments from orthopedic surgeons, others in the clinical practice, that basically referred to what they said that the regulation was proposing that all bone products be medical devices, which was not in the regulation, so it was very difficult to understand what the actual issue of those comments were.

Other supported or were against regulation bone allograft as a medical device, they said, and were specific in saying that mechanical shaping of bone is minimal manipulation.

Other concerns with the regulation of bone per se stated that these regulations, when they are final, would curtail supply of bone products, they would increase the cost without increased safety. They also

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stated that there was satisfaction with the industry standards, the voluntary industry standards which were being followed.

Others said that manipulation of bone by shaping should not determine the level of regulation. They quoted a long history of safe use. Many of these were general comments and they didn't say specifically what types of bones, whether these were the ones that we have talked about before as far as being machined and shaped for a specific purpose. There were one or two that said that FDA lacks the authority to impose premarket approval oversight on allograft bone.

There were again many comments which were specific to the bone dowels that came into our donor suitability docket. This was after the issues that Aric just talked about and the proposed panel meeting that came during this period.

Again, we had either support or comments against regulatory evaluation of machined or formed allografts as devices. We had support or non-support for regulation of allograft for procedures requiring stabilization, i.e., and spinal fixation.

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We had comments that said that the pre-machined dowels are superior to those machined in the operating room or they indicated that mechanical shaping again is not more than minimal manipulation. So, this was specific to bone dowels.

Other comments specific to bone dowels, again, had a major problem with any type of regulation that would be based on kick-up factors that were based on the shape of the bone per se. Shaping of the bone by the manufacturers should be regulated the same as shaping by the surgeon.

Other claimed that the bone allograft, bone dowels were superior to similar metal devices which had now been approved by FDA. Other comments said that these bone allografts should undergo the same degree of regulation as is required by these metallic implants.

So, the conclusion that I was able to pull together from these is, number one, that you can't satisfy everyone, we have many conflicting views. One of the reasons we are here is to try to get more information, so that we can understand what those views are.

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It seemed as we read through a lot of the comments, especially to the donor suitability, that a lot of the comments there were based on misinformation which was spread by certain interested parties, certain information, as I mentioned before, that these regulations would regulate all bone allografts as devices, and there were also those that said that we were going to be interfering in what surgeons do in the surgical suite.

So, the conclusion another reason that we are here, we need more information on bone allografts and their clinical uses. We would like some assistance in clarification of the definitions, and we would also like suggestions and some information that we could possibly use for technical guidance in the future to help us and help you to understand what our intent is as far as where we would kick up some of these products or whether we would or we would not.

So, thank you. I would just like a quick opportunity to thank those that helped organize this meeting including Ruth Solomon and Aric Kaiser, and from our Chief Counsel Office, Areta Kupchyk, and especially

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to Cathy Eberhart, who has done all the administrative details in getting this meeting together in a very short period of time. So, thank you.

Kathy.

DR. ZOON: Thank you, Martie. Again, my thanks to all who put this meeting together and particularly for the excellent presentations that we have heard this morning, so thank you to all the speakers.

We are ahead of schedule, but perhaps before we break, there might be a few minutes or an opportunity for questions to clarify any points made by the speakers.

So, if there is anyone who would like to ask some of our speakers for clarification of any of the points they made, please, this is your opportunity to do so. We would love to hear from you. So, don't be shy.

MR. RUSSO: I am Richard Russo speaking from AATB Governmental Affairs. This question is directed to Aric Kaiser.

With regard to your deliberations about what types of bone products, bone tissue-based products might fit the category of devices, were these deliberations part of a record that we could look at to understand the

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type of thinking that you were considering, or is that type of thinking more or less so historical, it really doesn't have relevance to today's conversation?

MR. KAISER: It is historical in the sense that it happened about a year ago, and it would certainly have some relevance because the things that were talked about internally and that we also got public comments on do relate to what we are talking about today.

So, as far as getting some information, certainly there is things that were sent in as comments to us related to that canceled meeting that could be requested, but other than that, there isn't anything official.

MR. RUSSO: Would it be possible to write for the informal comments or notes that you had, just so that we could be better informed?

I think one of underlying difficulties in our dialogue today has been the assumption and presumption and misinterpretation of what has been proposed by the agency or thought by the agency, and it would be help for clarification, I think.

MR. KAISER: I would say that most of the

comments that we got in relation to the canceled meeting are the same types of comments that have already been submitted to the docket for the proposed regulation. So, if you have got those comments or want to get to those comments, it is the same type of information that we had in response to the meeting that wasn't held last summer.

MR. RUSSO: Thank you.

DR. ZOON: The dockets, you obviously have access to the dockets to see that. Clearly, that would be something that could be shared.

DR. KITCHEL: I am Scott Kitchel. I am an orthopedic surgeon from Oregon.

I am wondering if there has been a working definition established for the two terms "homologous use" and "minimal manipulation," that we are using as a starting point or if that is still just a completely open question and that is what you are here for today is to try to gain some understanding as to how you are going to pin those terms down.

DR. ZOON: Right. In Dr. Solomon's presentation, she presented the definition of homologous and non-homologous. Ruth, if you would like to reiterate

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those or if you would like to show those again, we can do that, but again, part of the discussion here today is to even with making definitions, there is still a gray area, and I guess part of that is trying to set boundaries. So, I will ask Ruth maybe just to review that to make sure everybody is clear on that.

Ruth.

DR. SOLOMON: As I mentioned in my talk, the definitions that we are using were set up the establishment registration proposed rule, and those are the ones that we are still working with, and they include 1271.3(d) homologous use, which was divided into two parts, one for structural tissue, which we are talking about today, and the other for cells and non-structural tissue.

So, homologous use means the use of the human cell or tissue for replacement or supplementation and for structural tissue occurs when the tissue is used for the same basic function that it fulfills in its native state.

For minimal manipulation, again, it was a two-part definition, but we are particularly focused on the first of the two parts. So, minimal manipulation

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means for structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement.

I would just like to mention that the definition of human tissue for transplantation that Dr. Pereira shared with you, that is, in the final rule, basically, it is meant to cover these same two ideas.

The definition in the final rule says that human tissue, it cannot be considered a human tissue if you change -- here we use the word "alter" -- but if you change tissue function or characteristics, in other words, if you recover, process, store, or distribute a tissue by methods that change tissue function or characteristics, then, you are no longer considered a human tissue.

So, today, we should look at how the bone allografts fit under both the definition in the final rule of the human tissue and the proposed criteria put forth in the establishment registration proposed rule for when a human cellular and tissue-based product can be regulated solely under 361 as a tissue.

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DR. ZOON: Thank you very much, Ruth.

Please.

DR. FRANKEL: I am Victor Frankel. I am an orthopedic surgeon in New York and a member of the board of the Musculoskeletal Transplant Foundation.

Has the Orthopedic Panel had a chance to discuss these matters, and if so, what conclusions have the Orthopedic Devices Panel come to?

MR. KAISER: They haven't. That was actually going to be the meeting from last summer.

DR. ZOON: Please.

MR. BLOCK: My name is John Block from Telos. I have a question about what is up on the overhead now with regard to minimal manipulation and processing.

What is the purpose of the processing? I mean are we talking about microorganism inactivation, bacteria or viruses, or preservation, and when is that required or recommended?

DR. ZOON: Ruth, do you want to comment on that, please?

DR. SOLOMON: Sure. Processing is not required or recommended. It is just part of the definition of how

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we would view a product as a tissue versus as not a tissue. In other words, the interim rule, as Dr. Pereira explained, and the final rule, both tried to get across the idea that if you process solely to prevent infectious disease, contamination and cross-contamination, or to preserve the tissue, so that it can be utilized, it can meet its function.

If you do those two things, then, we consider that minimal manipulation and you come under the definition of a human tissue under the final rule and of the 361 product under the proposed approach. In other words, you are processing so as not to change the relevant characteristics of the tissue.

As I said, under the interim and final rule, this was focused on preventing contamination, preventing of disease transmission, and preserving the tissue.

DR. ZOON: Yes. If you could take the mike and identify yourself, please. You can come up here if you wish too, whichever is easiest.

MR. BARGANSKI: Simon Barganski [ph] at Allosource.

I have a question about the word "location" in

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the homologous use definition. As you know, most traditional bone allograft products are used in recipients in other locations from where they are taken at the time of donation.

I wonder if you could elaborate a little bit on when you say "location," whether you mean direct, one-for-one use of a donor tissue in an analogous site in a recipient.

DR. ZOON: Ruth.

DR. SOLOMON: Yes, that is what we had in mind in a location where such structural function normally occurs. When we are talking about the spine, our interpretation -- and we are here today to hear your interpretation -- our interpretation was that if you took bone, let's say from a long bone, and used it in the disc space where bone does not normally appear, the disc is quite a different material than bone, it is a soft material, and if you used the bone in the disc space for the purpose of connecting two vertebrae as in a spinal fusion, that would not be considered a location where the structural function of bone normally occurred.

Now, again, we are here to discuss that, but

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that was the initial thinking that went into -- it was discussed at the Tissue Reference Group, and those were some of our initial thoughts. Again, we are here today to hear your interpretation.

MR. BARGANSKI: May I just have a follow-up on this?

DR. ZOON: Is it a clarification?

MR. BARGANSKI: A clarification. In using your example, then, a device, say, that might be regulated in that particular indication as a Class III device because of its use, you are making a distinction and saying in the case of this tissue, because it is being used in a different location other than what is normally present in a pathologic condition --

DR. SOLOMON: Right, in the donor.

MR. BARGANSKI: So, that is the distinction you are making rather than a distinction that you would make how to classify a device, be it a Class I, II, or III device.

DR. SOLOMON: Right. That is quite a different -- what we are talking about today is, as Aric mentioned, along the spectrum from being solely a tissue regulated

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under Section 361, where a premarket application would not be required, that is one end of the spectrum, to the other end of the spectrum where you would be considered a medical device and have to submit an application.

What we are trying to do is find that bright line which may not be that obvious as to where we could distinguish between those products that would fall on this side, toward the tissue side, and those that would fall toward the device side, and what can we use to draw that line in the sand, so to speak.

So, that is really what this meeting is about, not so much of once you have determined that it is a device, whether it is a Class I, II or III, we will not be talking about that today.

MR. KAISER: That is actually a second question, the first one being are you a device or are you a tissue, and then if you are determined to be a device, you then enter a whole other realm of questions of where do you fall in the regulation of devices, I, II, or III.

QUESTION: I have a question. How do you classify, for example, umbilical vein if you don't have the possibility to transfer to the umbilical cord, you

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know, you are taking a vein from a tissue which appears only in the pregnancy, and then you transfer into a body, how would you match with the situation here?

DR. ZOON: Can I just say that the focus of this particular workshop is on bone allografts, and we would be happy to talk about other issues, but I think for right now if we could keep the focus on the question on the topic.

If one of the panel members wishes to discuss this, that is fine.

Please.

MR. STROBEL: Bruce Strobel of the Musculoskeletal Transplant Foundation. A follow-up to Simon Barganski's question.

The most commonly used tissue in the country by far, by any tissue bank in the country, is cancellous chips, and cancellous chips are sort of the standard of all tissues. Cancellous chips come from primarily the femoral head and the condyles, and that is where tissues are recovered, tissues are processed to product cancellous chips.

Cancellous chips are not used I would say

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probably 99.-something percent of the time, they are not used in the femoral head or in the condyles in their application. They are used many other places throughout the body.

So, if you take a strict interpretation of tissues being used for the same basic function that it fulfills in its native state, in a location where structural function normally occurs, I would venture to say that 90 percent, 80 to 90 percent of tissues that are distributed by tissue banks today, and have been for years, would not qualify as a tissue under that definition.

Any comments?

DR. SOLOMON: You are taking the most strict interpretation. I don't think we meant to be quite that strict. In other words, when you are taking the cancellous chips, are you not putting them into a location where bone normally sits? In other words, bone to bone. It doesn't have to be the same bone, but bone from a donor going into a location in the recipient where bone normally is found is what we had in mind by that.

MR. STROBEL: Right. But different types of

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bone for different types of function, if you look at the fusion referred to earlier, where putting bone where a disc is, that is the intended purpose. You are not trying to replace a disc, you are trying to fuse two bony segments.

So, that is the intended purpose, that always has been the purpose. You are not trying to replace a disc with a bone. So, in that sense, you have a question of is that the same function, the same location. You are not again replacing a disc, you are fusing bone, and that is the purpose of the bone, and has historically been the purpose of bone.

DR. ZOON: If I could just say that we are very anxious during the day to listen to a number of these discussions. The purpose of this session was really just to clarify the best we can, not to make definitions, because we are really here to listen and hear where the interpretation in some of the lines should be.

So, just for the sake of moving on. One last question for clarification?

MR. SANDHU: I am Harvinder Sandhu from New York at Cornell Medical Center. I wanted to follow up on that

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last statement.

I think it is a very important point that he raises, and I am still confused with the definition. One of the common uses for cancellous bone is not for bone repair, but for fusion of wrists, ankles, knee disorders, and so on.

Also, cancellous bone is often used for cortical disruption. So, I am still not sure on how we are applying that definition to these applications.

DR. ZOON: Thank you for raising that. I think part of the discussion today, if people could comment and continue to give input in that consideration, it would be very valuable.

What I would like to do, because of the time frame, and I know for those of you who would like to get a cup of coffee, it takes longer than 15 minutes in this places. So, I would ask that we break now and then reconvene at 10:05 for Session II.

Thank you very much and we appreciate the input. I would like to thank the speakers this morning.

Thank you very much.

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SESSION II

Professional Associations' Overview of Bone Processing and Clinical Uses in Orthopedic Surgery and Neurosurgery and Public Discussion/Comments

Moderator: David W. Feigal, Jr., M.D., MPH

DR. FEIGAL: Let's start our second session. It is pretty unusual to have a meeting that is still running on time at this point in time, and not hopelessly behind.

One announcement that I have been asked to make, as you may now, the Center for Devices and Radiologic Health regulate cell phones, and there has been quite a bit of controversy about that. One of the things we can't do is tell you not to use them, but actually we are going to tell you not to use them anyway in the auditorium because it is a little bit distracting.

Let's begin the second session without further ado. Our first speaker this morning will be Richard Russo from the American Association of Tissue Banks.

American Association of Tissue Banks

MR. RUSSO: Thank you.

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I have been asked to speak about current methods of bone processing. This does not address issues specifically of homologous use or minimal manipulation, but instead was intended to set out the general practices currently in use by tissue banks in general and specifically those that are accredited by the American Association of Tissue Banks.

So, the purpose of this overview is to quickly outline the general technical approaches for the processing of allogeneic bone and then to identify more concretely the specific methodologies currently in use by tissue banks accredited by the AATB.

It is not intended to be an exhaustive itemization of the methods and technologies in use as that would require more time and somewhat of a different format than we have available to us.

Tissue banks generally employ a method that utilizes a disinfection and cleaning process that is merged with the physical cutting and shaping, sizing, and other physical preparations of bone, so we have essentially two broad lines of activity going on at the same time.

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After the issue is initially cleaned and/or debrided with operations, such as high-pressure water debridement or manual scraping and cutting, the bone tissue passes through processing steps, such as washing, soaking, sonication, rinsing, and/or the pressurized flow of water and other agents to progressively remove and control bioburden and to remove physical components, such as residual soft tissue, cells, blood, bone marrow, and lipids.

Concurrent with or after this progressive disinfection and purging, the physical alteration of the tissue to shape, size the tissue, or to modify the surface of the graft is performed.

Techniques, such as cutting, sawing, grinding, milling, drilling, lathing, and other similar activities are performed to ready the graft for use as requested directly or indirectly by the surgeons.

As a parenthetical note, I should add that typically, tissue banks have specifications to which they produce these grafts, and they have developed them in response to requests for surgeons.

Sometimes after this primary processing has been

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completed, additional processing, such as complete or partial demineralization is performed to further modify and/or refine the physical characteristics of the tissue.

This type of secondary tissue processing is performed by over half of the AATB-accredited tissue banks that process bone tissue, and the specific techniques used in this type of processing, as well as the final specifications for these grafts varies somewhat among tissue banks. Inactive excipients are occasionally also added by some tissue banks to improve the handling of physical characteristics of these tissues.

These tissue processing activities generally take place in a controlled environment, such as a clean room or under a laminar flow hood. Tissue banks often utilize isolation or other techniques adapted from aseptic processing approaches used in the production of other types of medical products to the extent that these techniques are feasible and useful.

Tissue banks may or may not subject these grafts to terminal sterilization methods to achieve sterility.

As can be seen from the above comments, it will be even more clear in the following comments, there is a

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spectrum of approaches and basic methods used in the processing of bone tissue. FDA should be aware that in some cases, individual tissue banks use more than one method.

For example, in the issue of sterility, they can use terminal sterilization with irradiation or with ethylene oxide or don't perform terminal sterilization. These practices reflect the customer base of the individual tissue banks, such as surgeons, who may have a distinct view on the type of processing that they wish employed on the tissue grafts that they implant.

Now, to talk about some specific methodologies currently in use. There are at least six basic methodologies currently used to preserve and/or ready allogeneic bone tissues for clinical or surgical use.

These are freezing, cryopreservation, lyophilization, air-drying, full demineralization, and partial or surface demineralization. There exists a variation of techniques and specifications within the tissue bank community for each one of these basic methodologies.

Tissue banks use both manual and power tools and

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instruments to shape or size tissue grafts or to otherwise modify the surface or another physical characteristic of the bone tissue. The power tools and instruments can be hand-held or they can be table- or bench-mounted or floor-mounted. These can be drills and saws and lathes and similar equipment.

Sometimes hand-held power tools, essentially those used in orthopedic surgical procedures are fixed with table or set in a fixture to allow the bone tissue to be held and manipulated by an operator and subject to an in-place tool.

High-pressure water systems or wash systems rather are often used to debride tissue either as an alternative or supplement to other physical processing. Sonication and pressure-wash systems, positive and/or negative pressure systems are used to clean or treat the internal spaces of bone tissue.

Tissue banks use a variety of cleaning, wetting, and disinfecting fluids to process bone tissues. These include water, saline, surfactants, alcohols, including ethanol and grain alcohol, acetone, antibiotics, iodine preparations, hydrogen peroxide, hydrochloric acid.

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The water utilized can range from simple tap water to treated water including water that is labeled for, or meets the specifications for, water for injection. Excipients, such as glycerol, are sometimes used to modify the physical characteristics of the tissue.

Many tissue banks utilized modified or adapted aseptic approach to processing tissue in which sterile grafts are produced without the use of terminal sterilization, and terminal sterilization is also widely used. For this purpose, tissue banks utilize gamma irradiation, electron beam, and ethylene oxide gas to perform the terminal sterilization.

I should note that irradiation treatment is also sometimes used as a conditioning step prior to processing to control the bioburden of incoming bone tissue especially when no terminal sterilization process is used.

Tissue processing technicians are typically isolated or gowned. This isolation or gowning technique is sometimes as complete as it is for workers in standard clean room environments. In other situations, it is more

similar to what is found typically in an operating room environment.

The hard surfaces on which bone tissue is placed during processing are either draped or undraped according to the cleaning validations and procedures of the individual tissue banks or to the AATB-published norms.

Finally, I can mention the fact that if we view processing as a whole, tissue banks use a variety of different packaging systems, and they although directly germane, these include bottling, pouching systems, single, double and triple, wraps and tray systems.

So, that provides you with an overview quickly to what is being done with bone allografts today by the tissue banks in the United States.

DR. FEIGAL: Our next presentation will be by Dr. Laurencin and Dr. Jaffe from the American Association of Orthopaedic Surgeons.

American Association of Orthopedic Surgeons

DR. LAURENCIN: Good morning. This is a two-part presentation. Our first part is this morning, and we will be giving another part this afternoon. This morning, our charge has been to discuss allograft bone

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and orthopedic surgery, and give an overview of uses.

May I have the first slide, please.

This morning, we will just be talking about some of the uses in terms of allograft bone in orthopedic surgery. In the afternoon, we will get into a little bit more of the controversial areas in terms of definitions regarding minimal manipulation and homologous use.

Just in the way of background, I am a practicing orthopedic surgeon mainly focusing in areas of the shoulder and knee. I am Clinical Professor of Orthopedic Surgery at MCP Hahnemann Medical School and Professor of Chemical Engineering at Drexel University.

I have research interests which include bone regeneration and replacement. I have had some experience with working with the Food and Drug Administration with the Orthopedic Device Panel, and I am very privileged to be able to speak in conjunction with the American Academy of Orthopedic Surgeons.

When we think of autografts in general, we think about autogenous bone mainly from iliac crest. It really is the gold standard by which we compare other materials. It has an 80 to 90 percent healing rate. It is

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osteo-conductive, which means that it's a scaffold for regeneration. It is osteoinductive, containing a number of growth factors including bone morphogenetic proteins.

It is osteogenic, containing bone-forming cells, and osteointegrative meaning it can form a stable bond, and it is biomechanically stable as it has reinforcing properties, and again, it is the gold standard in terms of for bone repair.

But, of course, these are limitations that autografts have, and these are donor site morbidity, which is pain at the donor site, and this can be actually quite significant. Infection can also be a problem in terms of these donor sites, and it is interesting, over the last 50 years, that the reported complication rate of about 15 to 20 percent really hasn't changed in terms of pain and infection at the donor site.

There is also a limited supply in terms of graft. There is only a certain amount of graft that you can removed from a patient, and is especially a problem in terms of children. Also, there are issues of bone quality depending upon the patient's premorbid types of conditions.

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Allografts are tissues donated usually from cadavers. They are stored and processed in most cases in tissue banks and available in several forms.

As a matter of history, the first successful case of allograft transplantation was in 1878 by Macewen. Numerous reports in the literature followed over the next 20 to 30 years. In 1929, a paper on spinal fusion came out by Albee, and from there a number of papers have actually focused on the use of allograft bone in spinal fusion.

Shaped bone blocks for use in spinal fusion were reported by Briggs and Milligan in 1944, and there have been a number of papers that have come to the fore since then with the use of more shaped devices.

When we describe allografts, we can describe them in many different ways. One way is by type. We can talk about their being massive cortical structural osteoarticular, they can be cancellous, or they can be demineralized.

If we look at the uses of these allograft devices, we think about fracture care, spine, sports medicine, total joint replacement, and also tumors. My

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colleague, Dr. Jaffe, will be giving case presentations on these areas.

In the areas of fracture care, we have 6.2 million fractures in the United States each year, and approximately 500,000 bone grafting procedures are performed annually.

The majority of these are autografts, but approximately 150,000 of these are allografts, and this number is actually shifting where the numbers of allografts are actually increasing. The cost per graft is approximately 5,000, so there is a $2.5 billion health care cost that is involved.

When we think about the area of the spine, traditionally, it has had a number of applications in terms of autograft. Over the years, pre-shaped bone products have come to the fore. The pre-shaped bone products allows precision in design of implants. It obviates the back table approach in terms of shaping implants in the operating room theater, which cuts down operating room time, and a number of studies have demonstrated improved patient outcome probably because of the combination of the approaches, a combination of the

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reasons that we have talked about above.

In sports medicine, it has been traditionally used as part of reconstructive implants. The bone, tendon-bone allograft used for ACL reconstruction is a paradigm for that. There is a proven record of clinical efficacy in that area.

There are new generation of implants that are coming to the fore as shaped and preprocessed for use in such areas as interfering screws and other implants, and much of these areas are what we are going to be debating today.

I would like to turn the talk over to Kenneth Jaffe.

DR. JAFFE: Thank you, Cato.

What I would like to do today is to show you a little bit about my clinical practice. I am an orthopedic surgeon at the University of Alabama in Birmingham. My areas of interest are in orthopedic oncology and adult reconstruction.

So, the use of allografts is one of my main tools in my armamentarium of devices or structures, tissue, however you would like to classify that today,

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and I would like to go through some of the cases that I have done.

Areas that we use bone allograft is in tumor reconstruction after we remove a diseased segment of bone that may have some sort of neoplasm whether it be in failed total joints, and it is especially useful in revision of total joints after you see osteolysis in the bone and there is no bone to really hook up new devices.

We use it in traumatic situations, congenital deformities, and in spine fusions.

This is a defect that we see in the distal femur in which you have an osteochondral defect. One of the ways that we can rebuild that defect is with an osteochondral allograft. In this situation, what we would want to use is possibly a fresh allograft because of the preservation of the articular cartilage. This is the same defect with that osteochondral allograft, and in this situation, there is not a whole lot of good alternatives.

Other areas in total joint reconstruction, if someone has a congenital abnormality and which we don't have an acetabular socket big enough to put a prosthetic

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device in, and in revision surgery, this is a lady who had had four total hip arthroplasties, now her acetabular component is up in her spine. She has no proximal femur.

This is what I did rebuilding her bone in her acetabulum here. Here is a proximal femoral replacement. What we do is we can take bone. This is a femur right here. It is not used in its normal location, but I have bolted it to the iliac wing and then put in a acetabular component.

This is her walking with a cane, and she is quite able to do her activities of her daily living.

Other areas that we look at rebuilding bone is from traumatic defects, whether it be bone loss from the fracture, such as in this situation in which we do not have enough autograft to rebuild it. It involves the articular surface. Whether it be another situation in which it is a smaller injury, just involving the articular surface, or even in massive bone loss, this person was riding with his arm outside a window and hit a mailbox, this is an example of a distal humoral osteoarticular allograft, which it did include the whole joint, and the guy is playing golf again. He probably

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has a little higher handicap than some of us here who get to play more often.

Other areas that I am more interested in is in tumor reconstruction. We can use bone allograft to pack bone defects or even to reconstruct large segments as we do in trauma situations.

This is a unicameral cyst in the proximal femur. You see on the MRI the cystic changes. Here, we have a fibular cortical allograft, and this is demineralized bone matrix placed in here, as well as another fibular cortical allograft there, and this patient is functioning quite well.

This is a patient who I saw in fact yesterday, who had a resection of a distal femoral osteosarcoma, and this is his osteoarticular allograft at the end of his femur, and this is him able to bend down and to stand on that leg.

So, I have been able to salvage his leg instead of doing the time-honored procedure of an amputation.

This is another patient with chondrosarcoma of the proximal humerus. This is the resected specimen. This is the large, massive bone allograft. This is

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putting it into place. This is his function post-op.

In spinal surgery, and which you will hear more to day, it is used as a structural support and also to enhance fusions. This is a person with a lumbar compression fracture. You can see the bone in the canal, the massive destruction.

This is a fibula strut along with a plate in there to rebuild the spine, so it enhances the fusion and it also adds structural support.

So, these are some of the uses that I wanted to share with you about what we do as the end user of allografts and to give you an idea of what we are talking about from a clinical setting.

Thank you.

DR. FEIGAL: Thank you very much.

Our next speaker will be Robert Heary from the American Association of Neurological Surgeons.

American Association of Neurological Surgeons

Bone Allograft in Neurosurgical Practice

DR. HEARY: Good morning. I would like to thank

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the American Association of Neurological Surgeons for the opportunity to come here and speak to this group today.

What they have asked me to speak about would be the uses of allograft bone in neurosurgical practice, and what this basically comes down to is where we use it in spine surgery.

A point that I would like to clarify from listening earlier today is uniformly in spine surgery, every time we use allografts as a neurosurgeon, we are connecting two pieces of bone, one above to one below, spanning a place where at least a single intervertebral disc was located.

As such, there would never be a point that we would put bone in a place of bone in an isolated fashion. It will always be spanning a motion segment with the goal of that to be trying to obtain a fusion.

I would like to touch on some of the uses and importance of allograft bone, as well as the safety and some conclusions that can be drawn.

It is estimated that there are currently over a quarter of a million spinal surgical procedures performed yearly in the United States where allograft bone is

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utilized. In addition, there are greater than 200 peer-reviewed articles specifically describing the use of allograft bone in spine surgery over the past three decades.

We use allograft bone as a general rule to provide structural support. In addition, this can be augmenting or replacing autograft bone. Autograft bone has previously been mentioned. It typically is bone taken from the iliac crest although it can be taken from the lower portion of the leg in the fibula as well, but oftentimes there is a limitation in the amount of autograft bone that you can take from the patient themself, as well as whenever you take autograft bone it requires a separate incision being made in the patient with the attendant morbidity that can occur as a result of a second operation on the same patient.

The different types of bone we use are either cortical bone or cancellous bone. The cortical bone advantages are that it is rigid and provides immediate structural support when placed into the spine.

In addition, cancellous bone can be utilized, which allows for a trellis or lattice-like network that

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will be allowing bone to grow through this area, and that may be used either anteriorly or, more often, posteriorly.

Allograft bone incorporates by a total of five stages. These are the same five stages that autograft bone needs to go through when a fusion is to occur. Typically, inflammation will occur within the first 14 days after the fusion procedure has been performed, which is followed by a vascularization stage somewhere around 14 to 21 days this occurs.

Osteoinduction and osteoconduction occur, and these are at variable rates. Autograft bone tends to go through those stages a little more rapidly than allograft bone, however, the same identical stages are necessary to occur in order for a fusion to occur, and finally remodeling occurs.

The point of this is basically, although the two types of bone come from different sources, the identical process is necessary in order for a long-term bony fusion to be able to occur.

Surgery can be done either from the front or from the back, and for the purposes of this study, the

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majority of allograft procedures are done anteriorly.

The purposes of using the allograft bone when anterior surgery is one is typically to maintain height after removal of either disc material, possibly tumor tissue or infectious tissue, some tissue is removed from the front of the vertebral column, and there is a need to restore and preserve height, and that is accomplished with the allograft bone.

In addition to this immediate restoration of height and maintaining of anterior support, there is a need for a ventral incorporation or fusion to occur.

Posteriorly, there is occasional uses for a structural support although that is less common than the use of it anteriorly, as well as to augment fusion processes using it posteriorly.

When we need structural support in spine surgery, typically, it is with anterior processes needing one of the vertebra needs to be replaced or a disc between vertebra needs to be replaced.

The choices we have of what we can put in the space to maintain the structural support would either be autograft bone coming from either the patient's iliac

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crest or their own fibula, uncommonly done in the fibula, commonly done in the iliac crest, allograft bone available from the tissue bank, or metal instrumentation, which may be made of either steel or titanium.

An important concept to remember with spinal fusion surgery done in the neurosurgical and orthopedic practices involving allograft is that the long-term result requires that a stable bony arthrodesis or fusion occur.

Instrumentation, any of the metal products, be it cages, be it screws, hooks, rods, or any of those things, will eventually weaken with time. A bony fusion will strengthen with time, and that poses a very marked disparity between those two that devices, such as metal rods, eventually loosen up with time. It is a bony fusion that solidifies and takes the pressure away from the metal implants.

No instrumentation is able to take the place of a solid bony fusion or to obtain a successful result.

When the purpose of doing a spinal fusion of spinal surgery is to obtain a solid fusion, what we are interested in getting happened would be the bone, the

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allograft bone that we placed to fuse with the adjacent bone above and below it.

This will allow for long-term spinal stability to occur, it will allow for decreasing of the amount of pain, as well as a decreasing the amount of deformity or the potential for deformity if a stable fusion can be achieved, and it also can prevent potential catastrophic neurologic demise.

I think some of the tissue bank data has already been expressed but needless to say, there is a very exhaustive amount of work done prior to any allograft tissue being available to the neurosurgeon for implantation in the spine.

Fresh frozen or freeze-dried bone grafts are utilized in spinal surgery among neurosurgical practice. Tomford in 1995 wrote an article in the Journal of Bone and Joint Surgery showing that basically unprocessed bone has a very, very minimal risk of disease transmission, and basically processed bone, which is typically utilized in a neurosurgical practice, has essentially no risk of disease transmission with the current strict guidelines for harvesting of bone.

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I am going to present a couple quick studies that were mentioned showing the safety and/or efficacy of allograft bone. Grogen, in 1999, showed the use of allograft bone in scoliosis surgery and demonstrated this bone among 87 adolescent patients to be safe, reliable, an effective option, and found comparable results and clinical outcomes when compared to autograft bone.

Young and Rosenwasser utilized fibula allograft bone and found that there was less postoperative pain than what is utilized when autograft bone is employed.

Molinari, in 1999, and his group analyzed the use of autograft bone in anterior thoracolumbar spine surgeries. They had 67 patients and got a 98.5 percent incorporation or fusion rate. There were no episodes of graft collapse, and what they found was that there was no loss of structural integrity when they compared the immediate postoperative x-rays to x-rays that occurred at two and five years afterwards, thereby showing the utility of allograft bone for this purpose.

I think this is the most important point right here with respect to allograft bone. In addition to decreasing operative time, you eliminate the donor site

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morbidity.

I myself have personally presented information both at the Joint Spine Section in Neurosurgery, as well as at the American Association of Neurological Surgeons, where a large study was performed of over 200 patients where what we did was analyze pain postoperatively and we spoke to the patients.

I spoke to them for a period of four years asking them about the pain they had from autograft bone and recorded their answers and found that 92 percent of people said they had no pain. When people distinct and separate from my practice called the patients seven months apart from the average time when I had called them, my time was a mean of 12 months, the study time was a mean of 19 months, three separate people calling my patients blinded to me found that 66 percent of people said they had no pain and 34 percent of people had pain.

This was a high statistically significant difference and what it showed is that many, many patients are having pain, about a third of all people, autograft bone is taken. Oftentimes they may not relay that information to their surgeon for a variety of different

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reasons, however, I think when we are analyzing how much pain people are having, we have to look at blinded outcome studies.

This information has been submitted to the Journal of Neurosurgery, and I am sure it will be published at some point in the near future. The bottom line of what it let us know is that more people are having pain than are letting us be aware, and as such, my practice has changed as a result of that study to incorporate additional, more widespread use of allograft bone which does not cause the patients to have the degree of postoperative pain.

In addition, infection is possible, cosmetic deformity, blood loss and structural weakness are all possible things that can occur whether the bone is taken from the more common site in the iliac crest or the less common site in the fibula, down at the lower portion of the leg.

In addition, when you put in allograft bone, you are better able to evaluate a fusion compared to when you use metal implants, which make evaluation of fusion status somewhat difficult.

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As a summary of the use of allograft bone in a neurosurgical spine practice, this has become the standard of care in the community. There is a long history of successful surgeries, and the practice has been shown to be safe and efficacious for over 50 years, and my belief is that the use of allograft bone should fall under the category of medical judgment.

Thank you.

DR. FEIGAL: Next, Dr. Scott Kitchel from the Orthopedic Healthcare Northwest will make some comments.

Orthopedic Healthcare Northwest

Human Bone Allograft in Lumbar Spine Surgery

DR. KITCHEL: Good morning. Indeed, I am Scott Kitchel. I am an orthopedic spine surgeon from the University of Oregon. I am here at my own expense to try to represent my thoughts about this, and hopefully, also my patients and some of my colleagues.

I am going to try to center on human bone allograft in lumbar spine surgery, however, I must say that I am concerned by the topic of the entire meeting that the spine is somehow being differentiated, and if you look at the official posting of the name of this, it

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seems to call into question particularly the use of these products in the spine, and I think really we need to look at a more general topic of the use of bone allograft in all orthopedic applications.

The points that I would like to try to make in the next few moments are that spinal bone is really no different from bone anywhere else. In shorthand, bone is bone, if you will, what my perceptions are of what minimal manipulation should be considered going by the definitions that I have seen this morning, what I would consider homologous use, and a reiteration that bone is really used for grafting or to make bone grow to other bone. Bone isn't used as a disc replacement or bone isn't used as a joint replacement, bone is really put where you want bone to grow, so it is bone being put in a position for bone.

I think we might all benefit if we go back and think a little bit about bone in the practical terms of how we are using it for bone grafting. With apologies to the bone physiologists, really bone for bone grafting has two purposes, and one of these is structure, which comes from dense cortical bone or the outer lining of all bone.

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This happens to show the femur. The other is cancellous bone or the lining bone inside of that cortical bone, which really acts, as has been mentioned, as a scaffold for bone to grow.

Those are the only two real kinds of bone there are, and if doesn't matter whether that comes from the femur or the tibia or the spine or the skull or any other bone in the body. Again, I think it is important to remember bone is bone, and it is either cortical or it's cancellous.

We routinely take iliac crest bone autograft and put that into the spine, and I guess I am confused by this most strictest definition of homologous use. To me, that would go outside of what is homologous use, and I think that is a mistake. We are taking bone we want to have new bone grow through. We are putting into a structural position. It is structural bone, and it is allowing bone to grow. So, to me that should be homologous.

It is every bit the same as when we use allograft femur to replace a tumor in the lumbar spine. This time we were taking the part of the bone that indeed

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represents the structure. We are putting it where we need structure to get bone to grow from bone to bone. Even though it's a femur, it is still bone and you are getting one bone to grow to another. So, to me, that represents homologous use.

The definition that I was shown this morning when I asked that question is that it has to provide the same basic function. Indeed, in all instances, the same basic function is the support, so that bone can grow solidly together.

This is a picture of a piece of allograft bone from a femur, again with my apologies to the bone physiologists, this is what bone looks like when it is dead, and even autograft bone, once it has been harvested, is essentially dead, the osteocytes die, but it's a stroma of connective tissue with cells in it that are originally the osteocytes and osteoblasts.

The reason that I put this up is that again this is a piece of allograft. This is a piece of harvested autograft, and I would defy anyone in the audience to be able to tell me, if I hadn't told you, which one is allograft and which one is autograft.

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Autograft is just as dead as allograft by the time we put it into the body. So, to begin to try to differentiate between allograft and autograft, as it is used particularly in the lumbar spine for either structural support or a lattice for bone to grow through, I think is an artificial definition, and the one that we probably need to try to get away from a little bit.

Switching topics a big to minimal manipulation, this is a drawing from a surgeon by the name of Vich in 1985, and this was where threaded cortical bone dowels came from. This is a drawing of a bone dowel that he harvested off the iliac crest.

He then, with his own tap and dies set, cut these threads manually in the operating room, estimated that it took him about 30 to 45 minutes, and through that felt that he was gaining much better pullout strength and better mechanical properties of the bone by how he was manipulating it in the operating room.

Well, that 30 minutes cost us increased time, the wound is open, so there is an increased risk of infection, and certainly this technique is less precise than were available for today, but even considering all

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of those things, and again going back to the definition of minimal manipulation, or of manipulation, I don't think it alters the original relevant characteristics of that bone, and that was that definition that we were shown.

Can we do better than that? Sure, we do better than that all the time now. This is clean room processing of allograft bone. The bone is processed in a hypersterile condition. The most modern possible sets are used with taps and dies to cut it very precisely.

You wind up with this, which is a threaded femoral cortical bone dowel, certainly a more precise and a little bit more elegant implant than what Dr. Vich was cutting on his own, but I would say that it's not significantly different. Again, I don't think even when this is done commercially that this in any way alters the original relevant characteristics of the tissue.

Still, it is there to provide structural support. Bone is bone. This happens to be a femur going into the spine, but as a spine surgeon, that to me meets the definition of homologous use. I am putting a piece of structural bone where I need structure to occur.

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This is just another look at the spine. If we look at the spine, the bone that we used is almost always to try to make these vertebral bodies grow together, and I won't belabor that because several other people have said that this morning, but we tend to use structural pieces in these interbody positions, between the vertebral bodies. We tend to use cancellous pieces more posterolaterally with an attempt to try to get bone to grow through that lattice.

But again, whether we are using allograft or autograft, and whether it's iliac crest or fibula or femur, whether it has been machined or not machine, to me, those are all homologous uses because they all have the same basic function, and that is to fulfill the goal of getting bone to grow solidly to bone. In some area, structure is also needed, hence, the use of cortical pieces. In other areas, all you need is that lattice for bone to grow, and that is when cancellous is used.

Fusion can certainly occur in human beings without putting any bone into that area. We see spontaneous fusions in various degenerative conditions at all times, so it isn't even necessary sometimes to add

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bone or it may occur naturally without any grafting at all.

This is the insertion of one of the bone dowels that was earlier portrayed. Clearly, this cut piece and machine piece of femur providing structural support has been one of the index pieces allograft that has led to the interest on the FDA's part and whether or not this should be regulated.

But again, I would say that this is a piece of bone that is providing the structure. Often, this inner table will be packed with cancellous bone to provide that lattice, but in my definition, this is clearly homologous use because I am putting human bone into a human. I am putting structural bone into a spot where I want structure, and I am putting cancellous bone into the spot where I want it to grow, and at least by my definition, I have not functionally altered or clinically altered the significance of that bone by placing threads on it. I have merely improved the chances that it won't displace and have a complication.

This is what the bone dowels indeed look like radiographically when they are in place, and as the

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fusion begin to occur.

This is a schematic picture, again, that bone dowel in place in that interbody position. Again, I would like to stress not replacing the disc. Bone is not a disc replacement. Bone is there to provide structural support and a lattice to allow bone to grow solidly to other bone and create a solid piece of bone.

This is just an example again to show that bone can bridge without any implant. That is radiographic contrast agent in the disc space, but what is being outlined there is a bridging osteophyte, and that is a natural process and part of the degenerative cascade, and not reliant upon us putting bone into that inner space at all times.

So, the points again that I would like to leave you with is that spinal bone is not any different than any other bone. There really are only two types of bone - cortical and cancellous. Those occur in the spine, those occur in the femur, those occur in the skull, those occur in the radius and the ulna.

To me, minimal manipulation allows that I change that bone, whether I do that freehand in the operating

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room or it is given to me in a more precise manner, but again, going back to that original definition that I have shown, I don't think that that manipulation alters the original relevant characteristics of that bone, which to me are structural support and allowing bone to grow through it.

Homologous use, again, there is only two basic uses of bone in the spine. It is either structure or allow bone to grow through it. So, to me, any human bone being put into a position in the spine is by definition homologous use, because I am using either structural cortical bone or I am using cancellous bone to provide that lattice, and those will all grow together and allow a solid arthrodesis.

Just as a last point, again, bone is used for grafting and to make bone grow. It is not used as a disc replacement.

In conclusion, I would just urge that, as much as possible, the FDA consider this in the care of our patients. I know this is a very difficult and controversial topic, but I am concerned that there is going to be increased regulation which is going to lead

to more difficulty in obtaining these and ultimately not be in the best interests of my patients, both by decreasing the availability of these products and by increasing their cost.

Thank you.

DR. FEIGAL: The final speaker is this session is Jim Benson from AdvaMed. For those of you that haven't paid attention, formerly known as HIMA, and Jim once upon a time was one of my predecessors, so brings a long view to some of these issues.

Jim.

AdvaMed

MR. BENSON: Thank you.

As Dr. Feigal said, I am Jim Benson. I am Executive Vice President for AdvaMed. I have trouble saying that, I haven't gotten used to it yet. We were formerly known as HIMA, and are the largest medical technology association in the world.

I am here today because a number of AdvaMed members process human bone allograft and provide it to the clinical community. For many years, human bone allograft has provided significant clinical benefit to

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thousands of patients for a variety of disease states.

The of allograft bone in clinical practice is well established and has evolved over time through surgeon use, and to many, innovative and useful forms. AdvaMed advocates innovation for patient care through development of new medical technologies and products, however, we recognize that the regulation of these products is a challenging matter for the agency.

This morning I will present one possible mechanism for regulating these products. FDA has established regulations to address tissue products including human allograft bone under the authority of Section 361 of the Public Health Service Act and under applicable sections of the FD&C Act, as amended.

AdvaMed supports the regulation of human bone allograft as either transplanted human tissue or medical devices. Plainly, it is in the interests of FDA, industry, the health care delivery system, and most importantly, patients, for these regulations to be administered in a fair manner to achieve safe and effective products.

We believe that FDA must take great care when

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more than one center is involved with regulating human tissues or materials derived from such tissues to ensure that designated means of regulatory control for each product is, in fact, enforce. Only by doing so can the public health be protected and a level playing field among companies be created.

Our members report to us that despite efforts by the agency and the combination product law and regulation -- which I think I actually signed, didn't I, I don't know whether that was a good thing or not -- jurisdictional questions still abound regarding which FDA component has the lead for regulating human tissue and its derivative products.

We commend the agency's efforts to address this problem through the creation of cross-functional groups, such as the Tissue Reference Group, however, we have a few suggestions for strengthening the effectiveness of that group.

Specifically, we suggest improvements in the operation of the TRG. We encourage a more transparent and open process in its activities, including use of notice and comment rulemaking. Also, there is a need to

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ensure that product-specific agency decision-making is more open to public participation when it involves creating precedent for a product type.

This is particular important with the TRG because the group makes recommendations on individual products that may be binding for an entire product class. Public meetings should be held prior to making binding decisions that affect a class of products.

Additionally, the good tissue practices regulation needs to be implemented as soon as possible. The proposed regulation is encouraging and will be helpful to the tissue banking and processing industry.

When finalized, the proposed regulation will help to reduce confusion over the regulatory requirements necessary for companies working in this industry.

AdvaMed is appreciative of the effort that must take place to establish this regulation, but it is urgently needed now. We believe that finalizing this reg is critical before FDA proposes additional tissue-related regulations because of the agency's tendency to revisit each outstanding proposed regulation in light of the newest proposal.

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In other words, proposed regulations become a moving target that are unlike to be resolved as final until the target stands relatively still. Moreover, standards, such as the tissue engineering medical product, or TEMP, standards developed by ASTM will be helpful in providing continuing guidance for the industry.

Generally it appears that a regulatory framework for consistent, appropriate, and equitable regulations of human bone allograft either exists or is in preparation, but there is an urgent need for these regulatory elements to be completed and appropriately applied.

There is a need for a better and more encompassing definition of human bone allograft products to ensure that the TRG and regulated companies can more efficiently and predictably proceed in the future.

We recommend that homologous use and minimally manipulated criteria for determining whether a human cellular and tissue-based product is subject to regulation as a medical device or as a tissue be eliminated.

These agency proposed definitions fail to

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reflect the current FDA approach to regulating most tissue-based products as tissue. For example, the definition of homologous tissue states that such tissue fulfills in its native state, in a location where such structural function normally occurs.

This language is confusing. It appears to state that in order for a product to be regulated as tissue, it must be used in the same location from which it was removed and for the same purpose the tissue originally fulfilled.

The definition of minimal manipulation is imprecise, making it very difficult to draw a meaningful distinction between tissue-based products that are minimally manipulated and those that are more manipulated or more minimally manipulated.

Moreover, the result of manipulation should be more important than the fact of manipulation. Specifically, the shaping of bone, for example, into screws, wedges, pins, or dowels has not changed the character or identify of the bone, and should be seen as manipulation of tissue that remains tissue, and should be regarded as such.

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In other words, tissue-based products labeled "promoted for tissue replacement, construction, restoration of function" should be regulated under 21 CFR 1270 as human tissues. However, if false or misleading claims are made by the processor regarding the performance of tissue, then, the agency should enforce the Act against such persons or product.

In contrast, AdvaMed believes that tissue loses its identity when it is combined with a non-tissue component, such as combination products. For example, when bone is demineralized and combined with a device, collagen, for example, or a drug, then, it should fall outside of the tissue regulatory category.

From this, AdvaMed contends that FDA should consider deleting the homologous use and minimally manipulated concepts from the tissue definition and replacing them with a definition that reflects the current tissue versus device definitions.

By so doing, the agency will provide enough breadth to fairly capture the products of the future and ensure the safety and effectiveness of current products and those still developing in innovators' minds.

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If FDA is wedded to its proposed definition of tissue-based products, we strongly urge that the agency fully explore the meaning of its approach and include in the definition a range of examples that will clarify the scope of the term.

This is important to ensure certainty and not create regulatory delays and deny physicians excellent and needed products and ultimately hurt patients.

AdvaMed requests the agency to return to the primary goal as stated in the proposed registration rule - improve protection of the public health without the imposition of unnecessary restrictions on research, development, or the availability of new products.

AdvaMed recognizes that the regulation of tissue products is a complex issue. Although I have recommended one possible approach, AdvaMed would be happy to explore alternative approaches with the agency in a cooperative manner. I appreciate the opportunity to present our views to this forum.

Thank you.

DR. FEIGAL: I wonder if the panel could join us. The structure of the remainder of the session, and

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the only thing standing between you and lunch, is opportunity to have a little questions and answers from the panel, and if time permits, we will take some from the audience, as well.

Actually, I thought for a moment there Jim was going to propose that if you could say more than minimally manipulated for homologous use 10 times real fast, that you could have your product approved or exempted, but we will work on she sells seashells by the seashore next.

Questions from the FDA Panel

Let me start with a question while people are getting settled, and let me direct this at Richard Russo for starters, but anyone can tackle this.

Much of the focus of some of the comments have related to the possibility of transmitting infectious risk, and indeed that is an important part of the approach to tissue-based products, but another important part of FDA's role in consumer protection is to assure that products are manufactured with integrity and consistency.

So, if there is a product that is going to be

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used in a setting, and you want to know something about its tensile strength or time-to-failure, many of those types of things, most of which for devices is determined at the bench, it is not determined in clinical uses, there is a lot of attention to how do manufacturing methods affect product performance, and how do the tissue banks meet the challenge of knowing when they -- you know, you mentioned that there is many washes, debridements, different kinds of things that are done as you work with tissues -- how do you know, for example, if you choose to freeze something as opposed to another method of storage, how you have affected the performance of that product, the kinds of things that we would typically expect to see in an application for a product which says this is going to go, you know, your examples this morning have been largely in the spine to provide structural integrity for the spine, how do all of the tissue banks know what best practices are and if they have changed a practice, that it won't somehow affect the strength of the product or some other product characteristic?

MR. RUSSO: Thank you. I think that there are a

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couple of points to be made. First of all, the tissue banks that are accredited are to be validating the procedures. Now, that does not get submitted to AATB in the sense of an application similar to what would be submitted to the agency, but during the accreditation procedures, during the accreditation visits, the investigators review the validations that these people are performing, and they don't do it from the perspective of again looking at a label claim per se, but they look at the process.

So, validation is one of the basic methods. I think that another issue that you raised, though, that is implicit, needs to be made here.

The agency is proposing today something about some definitions. It becomes much more difficult to look at those definitions without the concept of label controls for Section 361 tissues because the only label controls that you really have at the moment are for "Section 351" tissues. That is what the whole debate is about.

So, we need to set into place the concepts that we would have for label controls for Section 361 tissues

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to make sure that they are adequate, because we have an unusual situation with allograft bone tissue, if I could just finish the comment here.

Synthetic devices were developed because of the shortage of allograft bone tissue. Bone tissue that was available was suspected to be unsafe for disease transmission primarily, and also was not viewed to perform effectively and may not be available.

So, many people spent a lot of time and effort to develop synthetic devices to approximate bone tissue. As bone tissue processing has improved and allograft tissue banking has become much more successful, and tissues much more widely available, we are taking the same concepts to look at tissue that we were looking at the devices that were intended to replace tissue, and we are saying, well, let's look at them all the same way, and it is kind of a circular argument.

If you start looking at a natural tissue transplant, and do not have enough of it, and you try to approximate it with a synthetic device, one understands the regulation of that.

What happens when you now have a tissue

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available, do you regulate it like you did the device? It is not really the same issue, but some of the same issues are involved.

DR. FEIGAL: Thanks for the comment.

Are there some questions? Kathy.

DR. ZOON: I have a comment and then a question. One, I want to thank the presenters this morning. Your presentations certainly were very helpful in understanding how the community, one, uses these products, and then some of the impact by the tissue banks and their control procedures, and Jim representing a number of the constituents who are manufacturing these.

Ultimately, the goal of this regulation in terms of FDA's controls here was to provide a risk-based strategy for a variety of different tissues going from very simple to very complex.

One of the issues, and clearly getting right down to the nitty-gritty, is the issue with bone dowels, because there you are right at the cusp of two technologies merging, and as I view many of the presentations this morning, as physicians and surgeons, you want reliable material.

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Your underlying assumption is the material that you are using is reliable. I think that is important because if you have defective material or material that didn't meet a certain set of standards, it would present problems for you and your patients as you were to use these materials.

The question is what are the appropriate standards, then, and expectations for those materials. Clearly, the impact of those I think, and what are those standards, are really the focus of this discussion.

I would actually be interested in the views of the panelists. If there weren't devices, if there weren't tissues, and we were just focusing on bone dowels, just focus, what are the important parameters, the important points that you would see in your community that would be important to you to ensure maximum success for your particular outcome, which would be patient health and safety.

DR. KITCHEL: I think to limit the discussion to bone dowels, the things that I would be interested in would, of course, be disease transmission, which you didn't really specifically mention, but I would want to

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know both the estimated and the actual risk of any sort of bloodborne infection or other disease transmission.

The second thing I would want to know would be something about the biomechanical characteristics of that bone dowel itself, and I believe you are aware, but the bone dowels that we are putting in the spine are tested to the same ASTM standards as the metallic implants that we put into the spine, and actually, their characteristics are known, their fatigue strength, their ultimate load to failure, and a good deal about their ability to stabilize the spine as compared to other implants.

So, that information is out there and has been done independent of the companies that are providing them to us. It has been done in research labs that are recognized.

I would also like to know something about the immunology of that bone as it is put into place, whether I should be expecting that there is going to be some sort of large immunologic or graft versus host response, and if so, then, what I might do or how I might better match that to the patient, so that I could have a better

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selection.

DR. HEARY: I think another point that might be worth making in addition to what Scott has said is that on our patients, what we are trying to do is prevent a difficult bad situation where something needs to be done, and I think we need to look at what the relative alternatives are.

I think that although it is important to specifically evaluate the allograft for itself, it is also important to recognize that the alternatives typically today include either metal, which will weaken with time, or autograft, which has some real morbidity to obtaining it, and with that thought in mind, I think it is more helpful to evaluate some of the regulations or lack of regulations with respect to allograft bone.

MR. RUSSO: From the tissue banking or AATB's perspective, I must say that when threaded bone dowels first became available, there was some concern I think among surgeons that possibly these cortical pieces of bone in the normal remodeling process might collapse and that there would be a loss of height, and that that would be a danger to the patient.

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What has transpired or what we have kind of thought about this, but haven't done anything about this, is that we now have tens of thousands of cases, and no real reports of this. To my knowledge, none of the tissue banks that are participating in this have had complaints about the collapse of the bone dowel and the loss of height, and I believe that the surgeons have said that that is an important criteria for evaluating an implant.

So, in this particular case, we arrive at a situation in practice where the theoretical concerns haven't been borne out. So, just possibly, maybe now is the time to take a careful look at what we are about to do because we are not pressed on a clinical basis.

DR. FEIGAL: Dr. Witten.

DR. WITTEN: First, I just want to make a minor comments because there has been such a question about spine in the title of the meeting, and that's just that we recognize that it is not just orthopedic surgeons that do spine reconstruction and repair. So, we thought we would make sure it clearly included neurosurgeons. I thought it may be helpful just to provide that

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clarification.

My question is no one has commented on the use of demineralized bone matrix in their practice, and I would be interested in hearing from the clinicians about that, how they use it, for what, what they mix it with, if they mix it with any autologous material from the patient, for example, and then a follow-on question, similar to Dr. Zoon's question, which is what type of product characterization do they think would be important for demineralized bone matrix.

DR. JAFFE: I use a significant amount of demineralized bone matrix in my practice in two areas. One is to pack defects, and I use it also in conjunction with allograft bone or with autograft bone as sort of a hamburger helper sometimes to expand the area.

The interesting aspects of demineralized bone matrix is its osteoinductive properties, and there are some commercial entities that are now commenting on their product has more of an osteoinductive characteristics than another commercially available product, and these sorts of questions and how they are making these comments, I do believe need to be addressed.

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Because demineralized bone matrix is osteo-inductive to other areas that we are using it in is to enhance fracture fixation or osteosynthesis in using it in the same way that we may use autograft bone, as well, and we are doing that for the same reasons that the spine people said with the pain, et cetera, from taking autogenous grafts.

So, it is a big portion of my practice of using that type of bone.

DR. FEIGAL: Would anyone else like to comment?

DR. LAURENCIN: I will be giving these comments this afternoon in my talk, but I think that just to sort of pre-reiterate what will be saying, there is a problem I think in terms of demineralized bone and other allograft bone materials in the measurement of biological potency, not only from the standpoint that different companies make different claims about the biological potency, but there are no standardizations in even some instances in terms of how biological potency is actually measured.

One of my slides from this afternoon says that if you are going to buy a tanning lotion that will have

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an SPF rating on it, but you can buy allograft bone and not really be sure what the potency of that material is, and when you look at what is up for grabs in each situation, you wonder why that doesn't exist.

MS. WELLS: We have some of the representatives of some of the associations here, and I don't know whether it will be part of the comments this afternoon, but I was wondering if we could focus a little bit on one of the questions that we asked for this meeting. Again if it is part of the presentations for this afternoon, then, fine.

We asked about industry standards, and it relates to another question that was just raised, just to get your opinion on what you think is the adequacy of what is available for bone allograft, and if you have any reflections on what you think could or should be developed in the future.

DR. LAURENCIN: I think, number one, I think that one issue is I guess there are no industrywide standards right now. There are standards that the American Association of Tissue Banks has, and many entities follow that, but in terms of standardized

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industrywide standards, they are not there. I think that is a major issue.

I think it is also going to be a major issue, and I think it is good that the FDA is looking at this situation right now, because I think over the next four to five years, as we see more processing methods come to the fore, more for-profit companies come to the fore in terms of tissue banks, there will be a number of different proprietary methods that will be coming to the fore for processing tissue that may not be available widely for other banks to use even.

So, I think there may be some difficulties in terms of that. So, I think there is a real gap in terms of development of industrywide standards that all banks will use.

DR. JAFFE: One of my concerns with the bone dowels is that these dowels are taken from usually the femur and patients age with osteoporosis being a major factor, can these tensile strengths be changed during the aging process, and do we have guidelines out there saying that the bone that is used to make these dowels should be under a certain age group, are there x-rays of these

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bones taken, or any ways to measure the densities before you are making these dowels.

That is one of the questions of an end user that I would like addressed from the industry that is processing these.

MR. BENSON: I think the ASTM standard I guess is in practice, and I don't know the extent to which that answers some of the questions. Well, you raised an excellent one, I think, in terms of bio -- I forget the term you used, not compatibility.

The thought I have is that maybe as a follow-up to this session, or I am not sure what the right forum is, if there could be a meeting of the minds of representatives of industry, of the profession, the clinical profession that is, with the agency and any other entities that are appropriate, to zero in on some of these problems.

In my opinion, the use of standards in the future is going to become much more important in this country. There are several legislative and regulatory reasons for that, which I won't go into.

So, I think that that can happen in a much more

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efficient and effective way of we kind of bring people together to address it. I think I can speak for our industry at least in saying that we would be delighted to participate in such a process.

MR. RUSSO: From an AATB perspective, I think it is important to remember where we are coming from. Maybe five to 10 years ago, specifically, the big concern, and up until very recently, the big concern has been disease transmission.

So, the standards that have been developed widely throughout the tissue banking community have been aimed at safety, and safety specifically in light of disease transmission. They did not incorporate the concepts that might be used in medical devices, such as a failure of an implant, that might be considered a safety issue.

So, from that perspective, we have minimum standards. From the perspective of performance -- and I hesitate to use the word "efficacy" because that is a 351 word -- from the perspective of performance, those standards haven't been developed. With the lack of labeling controls for 361 tissues and, as has been

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mentioned, the development of proprietary grafts for proprietary processing, this is an area for the agency to address.

I will see that all the tissue banks start off with a nature-given or God-given raw material. The processing counts, it really makes a big difference. So this is going to be a continued vexing issue for people who try to use standards, and maybe some of the ways that FDA has used standards and maybe parts of 600 previously, but maybe if we look at it from the ISO perspective or other ways, that might work.

DR. FEIGAL: In the spirit of continuing to run this meeting on time, I would like to thank all of the speakers for staying within their time allotments this morning. I look forward to the comments this afternoon.

We will break now for lunch and reconvene at 12:20. Thanks very much.

[Whereupon, at 11:22 a.m., the proceedings were recessed, to be resumed at 12:20 p.m.]

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AFTERNOON PROCEEDINGS

[2:20 p.m.]

SESSION III

Public Discussion/Comments

Moderator: Celia Witten, Ph.D., M.D., CDRH

DR. WITTEN: I think we will get started. In this morning's session, we had an introduction to the proposed approach and some historical background regard regulation of human cells and tissues follow by a presentation from professional groups on bone processing and clinical uses of these kind of tissues.

This afternoon's sessions are going to be focused on asking for your views on these products in particular as related to the five questions that we put out in the announcement for this panel meeting.

Our first speaker today is actually a duo, Dr. Laurencin and Dr. Jaffe will be speaking from the American Association of Orthopedic Surgeons, so I am going to turn it over to them.

American Association of Orthopedic Surgeons

Bone Allograft in Musculoskeletal Repair

DR. JAFFE: Thank you. What we would like to do

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today is to address the five questions that were asked to us as orthopedic surgeons and to get our views as to what we think of minimal manipulation, homologous use, and other standards, risks, et cetera, and Dr. Cato and I will address this. These are our views, as well as some of the views from the American Academy or Orthopedic Surgeons.

What we will do is to present to you what we see in real life situations.

The concerns that we have, one is preventing the use of contaminated tissue, what standards are available there as far as testing the tissues, et cetera, the proper handling and processing, how do we know that the methods that are used to manipulate these tissues will give us the qualities of the products that we really want, and the other issues are clinical safety and effectiveness.

So, the question we ask is how much government oversight is necessary to protect the public, and the issues that we also want to address is looking at donor consent and also how do you define procurement cost and then pass those on to the patient.

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So, we have gone over the definition of minimal manipulation, and it is the process that does not alter the original or relevant characteristics of tissue.

We have looked at the tissue in the reconstructive aspects, and so by processing it, we also want to know will it have the same function and characteristics. We also are not going to go through some of the extraction of the cells, but when we look at demineralized bone matrix, it is the extraction of a tissue product that does have biological activity, so this will fall into manipulation.

If you look at some of the other aspects of the bone dowels, we, as a group, feel that cutting, grinding or shaping of particular tissue is okay, that soaking it in antibiotic solution is okey, the sterilization procedures are okay, cell separation, as I mentioned, and the lyophilization or the cryopreservation or freeze-drying, we feel are okay.

So, what we do on the back table, is it any different than what industry does in their clean environment? One of the things that I think is important is that what I do on the back table, I am not as

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efficient as industry. Once I take a large piece of bone into the operating room, I essentially contaminate it, and there is a waste of some of that tissue.

So, industry may be able to take that same tissue, which is at a limited supply and have more uses for it than what I can as an orthopedic surgeon. So, we see it being used as a structural graft here.

When we talk about homologous use, I use allograft in the same connotation as where I would use autograft, and I personally think that homologous use should take those two issues into consideration and use it both for structural tissue and to enhance fusion.

So, more than minimal manipulation, there is tissues that are highly processed, and they are used in other than normal function and combined with non-tissue components and used for metabolic purposes.

Now, the issue that we ask on the demineralized bone matrix is that it is combined with other carriers or in a solution at times, so this, by definition, would make it more than a minimally manipulated product, but it has not been under any of the regulatory auspices as a device at the present time.

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Gene modification, activation, encapsulation, and cell expansion are other areas that are more than minimal manipulation, and it is a little bit more than the context of this conference is to go into what that entails, but once you take bone products and use them with gene modification, then, there should be specific regulations.

The demineralized bone matrix, we mentioned earlier do have osteoinductive properties, and certain companies are touting their products as to having more osteoinductive properties or can form bone better than others.

How are these claims substantiated, and what control trials are out there looking at the truthfulness of these studies is one of the areas we would like to be addressed.

Homologous use, we went over that, and it is in the same native state, in a location where structural function normally occurs. So, the bone graft acts as a structural support and enhances fusions, and this is an example in the spine in which you have a large segment of bone that is working in the place where bone used to be,

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as well as where discs are.

Now, Dr. Laurencin will proceed with his issues on bone grafts. Thank you.

DR. WITTEN: Before you get started, Dr. Laurencin, I neglected to say I am going to ask each of the speakers to state their name, their affiliation, which of course we already know, and also who is paying their pay, and this will apply both to those on the panel here, as well as anybody who asks questions from the audience.

DR. JAFFE: I am Kenneth Jaffe. I am a member of the American Academy of Orthopedic Surgeons. I am on the Committee of Biologics, and our committee is paying my way.

DR. LAURENCIN: I am Dr. Cato Laurencin. I am giving part two of my talk. My affiliations are with Drexel University, Philadelphia, and also I am a Clinical Associate Professor at MCP Hahnemann School of Medicine. I have been invited by the American Academy of Orthopedic Surgeons to speak, and they are paying my way.

First, to start out, I would like to thank the Academy for inviting me to share some of my views on the

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risk controls and standards regarding allograft bone.

First, I would like to just jump right in in terms of talking about some of the risks that are posed, and during my portion of the talk, what I would like to do is also see if I can start to address some of the questions that the FDA has posed to us and provide some answers and some of my perspective in terms of that.

First, in terms of the risks, we think about the effects of processing and sterilization, and their effects on biomechanical performance, and also the effects that can take place in terms of biological performance. This actually speaks to their question of what risks to health have been identified and characterized for human bone allograft products.

As we think about the risk of grafts, we first think about infection. Again, while the risk of infection and risk of infectious problems are low, one would think that the higher risk materials would be the osteochondral grafts because they have bone marrow that remains, and there is less processing.

Low risk are the cancellous chips and cortical struts, because a number of processes are used to remove

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marrow and have lower risk. What are the risks? Disease transmission, hepatitis B and hepatitis C again being tested for in a number of processes.

The AIDS risks. Right now in terms of bone, the risk for AIDS, the rates are lower than that for blood transmission. Approximately 1 in 450,000 chance in contracting the HIV virus through blood. There is approximately 1 in 1.6 million chance of contracting HIV through bone. There are no instances of HIV transmission through bone since 1985.

So, in terms of controls, for living donors, allograft tissue is quarantined for 180 days, and the donor tissue is retested before it is released. So, there are a number of controls that are there.

As I alluded to before, the issue about biomechanical performance and biological performance of the allograft, as alluded to earlier by members from the AATB, the initial concerns were really about trying to prevent infection, because that would be catastrophic in terms of being able to have allografts on the market, but these are very, very important considerations, and I want to leave a few points in terms of my talk.

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I think the biomechanical and biologic performance of these materials is very important and really needs to be evaluated.

We know that the freeze-drying process can affect the properties, sterilization methods, gamma, electron beam sterilization, even ethylene oxide can affect the processes involving its biological and biomechanical performance.

A number of processes combine freeze-drying and sterilization. Again, these can affect it.

This slide talks about the types of treatments and sorts of mechanical properties that have been documented, and this is in orthopedic clinics from 1999. We can see that with all the different processing methods, we can change our mechanical bending strength and elastic moduli from, say, fresh human cortical bone to the gamma-irradiated bone. We can see significant changes is bending strength and elastic modulus in terms of these sorts of materials.

So, depending upon the application, it is going to be very important to be able to characterize and reproducibly characterize that the performance of these

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materials are.

The biological performance of these grafts can be changed depending upon their processing conditions, and we pretty much know that. Again, the goals, the grafts should be at least osteoconductive, and most of the types of grafts actually make claims for being osteoinductive.

Osteoconductive, again we are defining it as it provides a surface area and provides an area for new bone and growth, and remodeling, and osteoinductive allows actually a source of inductive factors for regeneration of bone.

There are also the issues regarding an adverse immune response, and really, these graft materials, one should be able to characterize what the immune response is, and the adverse immune response should be minimized in terms of the clinical situation that is going to be present.

The question is what controls have been identified to adequately address the risks to health of use of these human bone allograft products. I have to emphasize, we must emphasize that we are talking about

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risks as we know them today, so while a number of claims are made that we have no history of any infections since 1985, and I may take a little bit of offense saying there is virtually no risk of infection from these sorts of graft materials mainly because again, we are talking about risks as we know them today.

There are viruses including slow viruses that we are getting more and more knowledge about, prions and some viral particles also that are there. I think that we can say that in our processing methods for our known disease pathogens that we have today, we do have good ways of being able to analyze them for them, however, we can't close the door in terms of the risks in terms of infection because I think this is a changing environment.

Obviously, if we were sitting here in 1981 at the same meeting talking about bone allografts without testing for HIV, we would say we have a handle on testing for viruses. Fifteen years later, we have more knowledge. I do predict that in 15 or 20 more years, we may be talking about another panel of different pathogens that we may be testing for in addition to the ones that we have cited here.

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Screening of donors, there are a number of adequate controls that are in place right now, screening of donors is important. There are FDA and AATB guidelines that exist, and they can eliminate approximately 90 percent of all inappropriate donors just from the initial screening.

Again, in an assessment that is performed, medical, social, sexual history inquiry that is performed. Interviews are conducted with potential donors, family history and genetic background, a minimum of three-generation history for any genetic defects.

So, again, a medical history review, cadaver donor, autopsy report, there are a number of different ways in which this is done. Disease testing of donors, we have talked about the panel of testing that is done, and FDA guidelines are indicated for several of the test methods that are utilized. In most cases, they must use FDA license test methods including blood tests, PCR tests, and RNA tests for that area.

So, a number of controls do exist in terms of obtaining donors.

In contrast, specific guidelines for allograft

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tissue processing at the industry level have not been developed. As I said earlier, this may become problematic as for-profit companies develop proprietary processes for a competitive edge, and I do believe that there is a need in terms of industry standards.

The next question is what industry standards for bone allograft products are available, what standards will be needed in the future. Again, I reiterate currently, there are no industrywide standards for allograft processing. There is the AATB standards that is followed by industry, however, these are not standards that are widespread and required.

There are also unaddressed issues that are there. First of all, for age, does the age of the donor affect the allograft, and there is a wide range of age that is accepted, and are there any thoughts taken into account in terms of the age range, in terms of the patients that are selected.

Biological activity. What is the cost of processing on the biological activity of the allograft? The current available information on the biological potency of these graft materials is actually very sparse.

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In fact, if one looks at a trade journal in terms of orthopedic trade journals, one will see infomercials or this is called an "advertorial." I guess it is sort of an infomercial comparing different methods of different types of graft materials.

Again, this is our literature, how information about graft materials are being brought about by companies that are sponsoring studies that demonstrate different graft materials and their potency.

Again, this speaks to the fact that really more work needs to be done in terms of defining, really defining what the biological potency of these materials are. As I said earlier, even skin tanning lotions have sun shield protection standards, SPF ratings. Should this industry have a BPF or bone potency factor provided for reference? I think that there should be for these types of materials.

In terms of consent, are the donors fully aware of what is being done with their tissue? I think that there is a wellspring of public sentiment that is coming about stating that donors may not be fully aware that their bone that they donate to their local bone bank,

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that they are hoping will help someone else in their community may be shipped to Germany, processed into a certain paste, and then shipped to another location or another country for use in an elective operative procedure.

Again, it may not be that at the time of consent, individuals need to have a consent sheet saying your bone may be sent to Germany, but that there must be ways in which we must educate the public as to how these bone grafts are used, how they are procured, and also where these bone grafts go.

In terms of cost, should donated tissue be sold for profit? We have the National Organ Transplant Act of 1984, which prohibits the selling of human tissue, but, of course, now with the processing and the preparation and the transmittal of these tissues have prices that are attached to them, and again, these prices that are given sometimes really don't correlate, in my mind, really don't correlate very well with the processing that is involved.

The whole issue about a gift for the person that gives becoming a product that translates to a $500

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million business is something that I think really needs to be examined, and especially in the concept of donor consent and where their bone is going.

Final comments. Should donor records be kept for 10 years? I do believe so, and I think that that may be part of the new standards that should be developed.

Should a sample of the donor tissue be kept for 10 years? I believe so.

Should there be a requirement to report serious errors and accidents? I do believe so, because I think that we haven't come to the end of our line in terms of knowing what sorts of biological hazards, what sort of performance hazards are present in bone grafts.

I also would say that I think this may be a shifting paradigm in terms of some of the biological properties and biological problems that may come with bone grafts in the future.

Should the FDA require the registration of all tissue banks throughout the country? Personally, I do think so. Why? Because it gives us a better ability to track trends and changes in bone banking that is taking place, and also gives us a better ability to communicate

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urgent information.

Urgent information that is obtained from the FDA at this point can be disseminated, but it may be quite difficult if there are bone banks that the FDA doesn't know about or has no power to regulate or control.

Formal standards for all tissue banks need to be obtained, and I think that needs to be done soon. Why? There is an example of the Pacific Coast tissue bank case in 1994, a case in which a Florida tissue bank was given a bone donor. They rejected the donor because the person was a cocaine user. The Pacific Coast tissue bank accepted the donor. Again later, a recall was ordered by the FDA, and the donor tissue wasn't used.

But again, this illustrates the fact that some formal standards, if two tissue banks, if one tissue bank accepts the donor, another tissue bank doesn't accept that donor, I think it is very, very important that formal standards for all tissue banks be obtained and utilized, so this sort of problem won't happen.

Now, in terms of doing this, how to carry this out, well, this has to be carried out in an alliance between clinicians, industry, and the American

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Association of Tissue Banks, and the FDA. I don't think it can be done with one organization alone in order for the system to be practical.

From a practical standpoint, in terms of inspection, I think it is going to be very difficult for the FDA to be inspecting all these different tissue banks, and it really has to be an alliance between industry and the tissue bank and the Association of Tissue Banks to be able to work with the FDA, to be able to do this.

Clinicians have to be involved because I think clinicians are very important in terms of deciding, as the end user, to decide what is going to be practical in terms of the industry being able to provide.

DR. WITTEN: I would like to thank our speakers and introduce our next speaker, who is Dr. Fessler, who is from the American Association of Neurological Surgeons.

American Association of Neurological Surgeons

Neurosurgery's Perspective of FDA Concerns

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DR. FESSLER: Good afternoon, everyone. I am Richard Fessler. I am here representing the American Association of Neurological Surgeons. Why am I representing them and why are they paying for me to be here?

By way of introduction, for the last 11 years I have a full professor in the Departments of Neurosurgery and Neuroscience at the University of Florida Brain Institute where I held the Dunspaugh-Dalton chair in brain and spinal surgery. While there, I was the Director of Education and Clinical Services, Director of the Spinal Cord Injury Center, and Director of the Hoff [ph] Neuropharmacology Laboratory.

Recently, however, I moved to Chicago at Rush Medical School in the Chicago Institute of Neurosurgery and Neuroscience where I founded the Chicago Spine Institute and I am the Director Minimally Invasive Surgery.

I interact with the FDA by participating in their Neurological Devices Panel and for AANS and CNS, I chair their Neurologic Devices Forum and their Drugs and Devices Committee.

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I would specifically like to address the five questions we were asked to address by the FDA, that is, what risks to health have been identified and characterized for human bone allograft products, which uses of human bone allograft fall within or outside of FDA's proposed definition for homologous use, which processing procedures applied to human bone allograft fall within or outside of FDA's proposed definition for minimal manipulation, what controls have been identified to adequately address the risks to health of use of human bone allograft products, and what industry standards for bone allograft products are available and what standards will be needed in the future.

Let's look at the first question, what risks to health have been identified and characterized for human bone allograft products.

I am not going to talk about theoretical risks, I am not going to talk about a potential infection that we might find out exists 25 years from now, that we don't know about now, what risks have been identified.

We have been using allografts since 1878, 125 years just about. This is just a sample of a few papers

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representing hundreds that demonstrate 90 to 95 percent success rates, and by that I mean successful fusion, no significant complications.

Most complications with allograft are surgical, they are not due to the allograft, they are due to me, the surgeon, so let's not blame my infection on a piece of tissue that I happen to use.

Estimated cases per year, 250- to 400,000. What is my primary alternative? The alternative I have is to harvest autologous bone or use cortical or cancellous chips. If I use autologous bone, I have an increased operative time, an increased blood loss, an increased operative trauma, increased pain, increased infection rate, increase hospital stay, limited supply of tissue that I can get from that person, all of that translates into a worse result and increased cost.

What if I use cortical bone like a fibula? There is significant morbidity if I harvest your fibula to fuse your neck, significant. I have decreased osteocytes that I can get from that, I have decreased osteogenic potential, I have less surface area to work with for fusion, and I have a variate vascular ingrowth

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compared to cancellous bone.

What is the complication rate if I just take your iliac crest instead of using allograft bone? Four papers over the last several years vary between 10 and 20 percent morbidity just by harvesting your bone. My complication rate by using allograft bone is 2 percent.

Therefore, relating to Question 1, there has not been identified a significant human health issue with the use of human allograft bone for use in fusion over the last century. In fact, there is significantly more morbidity if I use your own bone.

Question No. 2. Which uses of human allograft bone fall within or outside of FDA's proposed definition for homologous use? Remember, the definition. Homologous use means the use of a cellular or tissue-based product for replacement or supplementation and for structural tissue-based products, occurs when the tissue is used for the same basic function that it fulfills in its native state, in a location where such structural function normally occurs.

I highlight that because, as Dr. Kitchel pointed out, that is a critical misperception. Using bone to

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fuse bone to bone is homologous use. The disc doesn't matter. That is now why we are there. We are there to fuse bone to bone, and bone is bone, period.

It is illogical, nonphysiologic, and contrary to current medical practice to try and define it other than that. To specify that we should not use fibular bone homologously for fusion just doesn't make sense. It unrealistically limits physicians' best judgment to treat his patient and it results in decreased utility of tissue, probably decreased success rates, and increased harm to my patients.

Therefore, rigid location specification is illogical, it is unnecessary, it is harmful to public health.

Question 3. Which processing procedures applied to human bone allograft fall within or outside of FDA's proposed definition for minimal manipulation? Again, the definition means for structural tissue processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement.

We have a long history of using shaped bone, as

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has already been pointed out by Dr. Kitchel. This goes all the way back to 1944, so 55 years, we have used dried cortical wedges, we have used rings, we have used cylindrical dowels, we have used threaded dowels, we make them ourself in the back of the operating room.

As has been pointed out, I can't do as good of a job as can be done in a laboratory. I cannot do it time expeditiously, I cannot do it as sterily, I cannot do it as well. It causes increased morbidity for my patient.

The Federal Register of May 14th, 1998, said procedures that would be considered minimal manipulation include cutting, grinding, shaping, et cetera. This makes sense. To say that preshaped bone is just a materials change is absurd. That is an engineering concept. We are dealing with clinical reality.

To take this away from us would fundamentally change the practice of medicine. It would represent a major step backwards in patient care.

The advantages, why is that so? I told you if I use preshaped bone, I have decreased operative time, my technique is simplified, I have decreased blood loss, I have improved fusion rates, and I have decreased patient

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morbidity. Therefore, relating to Question No. 3, we have a long history of shaped bone and spinal surgery. Preshaping the bone does not alter its relevant characteristics or its utility for reconstruction, repair, or replacement. It is simply bone-to-bone fusion.

The designations in the Federal Register of 1998 are logical and useful. The proposed alternative new definitions are not clinically relevant. It has significant benefit to my patient for me to continue using this. Decreased access to these products would have a negative impact on public health.

Question No. 4. What industry standards for bone allograft products are available, and what standards will be needed in the future?

We began developing these standards voluntarily more than 50 years ago. We have numerous anti-sepsis techniques, sterile practices, and documented tissue handling procedures. The guidelines of the American Association of Tissue Banking of 1995 are voluntarily followed by everyone, and, in fact, the regulation on human tissue intended to transplantation of July 1997 is

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essentially almost a reproduction of those guidelines.

By the Federal Register evaluation, September 30th, 1999, estimated percent of entities in compliance with the industry standards are 100 percent.

Therefore, existing standards would quite appear appropriate for human allograft bone.

Finally, what controls have been identified to adequately address the risks to health of use of human bone allograft products? What we are really looking at here is the premarket approval process. Premarket approval would generally be required for tissues that are processed extensively, combined with non-cellular and non-tissue components, are labeled or promoted for purposes other than their normal functions, or have a systemic effect.

Allograft bone is not extensively processed. It is processed to the patient's benefit in a manner requested by physicians or done by a physician himself in the operating room. Standard bone allograft is not generally combined with a non-cellular or a non-tissue component.

Bone-to-bone fusion is the normal process of

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bone.

Finally, no systemic effect of allograft has ever been demonstrated. Therefore, existing controls would appear appropriate for human allograft bone.

What are the ramifications of redefinition? If redefinition initiates PMA 510(k) processing, the availability of allograft would immediately decrease. The requirements would likely result in many small companies going bankrupt or stop producing these products entirely.

The associated increase in recordkeeping would be redundant. It would make an already cumbersome recordkeeping system overwhelming. Therefore, the overall effect would be a widespread negative impact on patient care and public health.

In summary, the AANS and the CNS believe that bone products for spine fusion have a long history of safety and efficacy. Appropriate regulations for harvesting, preparation, storage, and use of these bone products already exists and have already been tested.

The availability of pre-shaped bone products results in decreased patient surgical time, surgical

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trauma, and morbidity, and use of pre-shaped bone products results in improved surface-to-surface contact, and therefore, potentially improved outcomes.

Patient access and availability of these products could be seriously harmed by overburdensome regulatory redefinition or reclassification. Current documentation system requirements very adequately protect patient safety as demonstrated by our history. Further requirements are unlikely to improve this, and such benefits could, in fact, cause extreme hardship for some of the tissue facilities that we get our tissues from.

Redefinition of minimally manipulated and homologous will have profound implications on human allograft availability with consequent negative impact on patient health.

Therefore, the proposed redefinition is medically illogical and contrary to our accumulated medical knowledge of the past 100 years.

Therefore, it is the opinion of the AANS and CNS that redefinition of minimally manipulated and homologous has no logical basis for medical justification. Furthermore, it has a high probability of harming rather

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than helping patient care and public health.

We strongly recommend the current definitions remain in effect.

Thank you.

DR. WITTEN: Thank you, Dr. Fessler.

Our next speaker is Mr. Robert Rigney from the American Association of Tissue Banks.

American Association of Tissue Banks

MR. RIGNEY: Good afternoon. My name is Bob Rigney. I am the Chief Executive Officer of the AATB, the American Association of Tissue Banks. I am accompanied here today by Mr. Richard Russo, the Chairman of AATB's Government Affairs Committee. We are pleased to present this statement on behalf of the AATB concerning human bone allografts and the FDA's emerging program for tissue regulation.

The AATB is an association with a public health mission. Our purpose is to promote the availability of safe and high quality tissues for transplantation. Our mission focuses on the development of standards for human tissues and tissue banking, the accreditation of tissue banks to ensure compliance with our standards, and

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educational and certification programs for tissue bank personnel.

Our membership includes more than 1,200 individual members and nearly 70 accredited tissue banks. Let me be clear. The AATB has long advocated and continues to support reasonable FDA regulation of tissue banking.

Over the years we have provided useful information to assist the FDA in addressing its public health challenges, such as disease transmission. We have worked with the FDA to develop an appropriate regulatory scheme in this evolving field of medicine. We intend today to continue that collegial and cooperative spirit and to suggest needed changes to the FDA proposed regulations for tissues.

The AATB has previously submitted comments to the FDA in response to the May 14th, 1998, publication of the proposed registration rule. At that time, we endorsed the proposal to require that all establishments that recover, process, store, and distribute tissue register with the FDA and list their products.

However, we reiterated concerns that we had

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voiced repeatedly since 1997 about certain definitions contained in the proposed regulation. Specifically, we requested that the FDA clarify the definitions of homologous use and minimal manipulation, that have major importance in the proposed regulation.

To date we have received no response to our earlier public comments and requests for clarification of the criteria. Our concerns about these criteria have grown to misgivings as we witness difficulties in the proposals to classify as medical devices, allograft heart vales, demineralized bone matrix grafts, fascialata provided for bladder repair, and threaded cortical bone dowels.

In particular, we fear that the proposed terms and criteria, if applied as written, may seriously disrupt current tissue banking operations, as well as surgical practices. The FDA's use of proposed definitions could lead to many allograft products being regulated under Section 351 as biological products or as medical devices regardless of the level of risk posed to patients or the long history of safe use of these tissues.

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Regrettably, therefore, we feel compelled at this time to reiterate our deep reservations about the inclusion of the two criteria as building blocks for the proposed registration rule.

The AATB accepts that some criteria for distinguishing tissue from other classes of products are necessary for the agency's regulatory plan. However, we also recognize that the criteria chosen could significantly affect the level of patient care and surgical practice, as well as current tissue banking operations.

Perhaps more importantly these criteria could strongly influence progress in these areas in the future. The AATB supports the proposed FDA registration of tissue banks, however, we cannot support the inclusion of the criteria homologous use and minimal manipulation.

We continue to encourage the FDA to finalize its registration requirement, nevertheless, we recommend in the strongest possible terms that these terms not be included in the final registration regulation.

The FDA's proposed goal strategies and perspectives were outlined on February 28th, 1997, in the

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FDA document entitled, "A Proposed Approach to the Regulation of Human Cellular and Tissue-Based Products."

This document sets out a risk-based, tiered approach that applies regulation in direct proportion to the perceived are likely risks to patients. The proposed approach is crafted to efficiently use the FDA's limited resources. It contemplates an establishment, registration, and product listing approach to cellular and tissue-based products.

It embodies only minor well-understood risks. It also provides for more stringent drug or device regulation for cellular and tissue-based products that do not meet the criteria for presenting minimal risk to patients.

As we have noted previously, the AATB supports in the main the concepts presented by the FDA in the Proposed Approach document. We recognize that the FDA approach requires the development and use of some criteria. These criteria allow the agency to correctly and to consistently establish which tissue-based products present well-understood and/or minimal risks, and therefore qualify for minimal regulation. However, the

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criteria described in the proposed regulation will work to undo the FDA's stated goals of a risk-based approach.

The AATB wish to contribute to the positive resolution of this situation. While reaffirming our concerns, we want to offer constructive guidance. We want o develop appropriate criteria that would address the agency's goals and our concerns.

We would therefore welcome the opportunity to meet with the agency to discuss criteria that would substitute for homologous use and minimal manipulation.

Thus far, the FDA has assumed that a tissue-based product can be considered to have an homologous use only when the tissue is used for the same basic structural function that it fulfills in its native state, a location where such structural function normally occurs.

This perception fails to account for the realities of modern surgical practice. Non-viable bone allograft tissues were used in more than 650,000 procedures last year, surgically repair or augment defects or to replace diseased tissues.

Surgeons selected these tissues because of the

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qualities or characteristics that might be useful to properly treat their patients. They did not simply rely on what an anatomy or physiology text might identify as the basic function of a tissue. In addition, the surgeons used the tissue where it was needed, not necessarily at the anatomical site from which it was recovered.

The FDA's criteria seems to be based on a misperception that ignores current standards of surgical practice in tissue banking. It implies that if a tissue is transplanted for the same use and in the same or analogous anatomical site from which it was recovered, then, its use is somehow more basic and less risky to patients.

The FDA evidently believes that only such use should be considered as presenting well understood and acceptable risks, and only grafts provided for such use should be regulated in Section 361 tissues.

This misperception fails to take into account the routine surgical practice of bone grafting where bone from one part of the body is routinely transplanted into another part of the body. In this application, the

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surgeon fills a cavity in a bony structure or construct with a bone graft taken from another part of the body.

The bone graft is incorporated into the skeleton and/or provides skeletal support. Bone grafts are also commonly used to fuse vertebrae in the spine and to repair the acetabulum in revision hip arthroplasty and to repair other damage caused by trauma.

Bone grafts intended for use in interbody spinal fusion are among the most common applications of grafting in orthopedics and neurosurgery. The FDA's homologous use criterion could lead to the conclusion that bone grafts do not fit within the definition of tissues because the joint space between the vertebrae is normally filled with a fibrocartilaginous disc, and not a bony tissue. The conclusion could result in disruption of the well-established surgical practice of spinal fusion for which the attendant risk of bone grafting are well understood.

A similar situation could occur arthrodesis of other joints. Furthermore, it would be exceptionally difficult to apply this regulation in a forthright and unbiased way since many different types of bone grafts

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are used in a variety of orthopedic and neurosurgical procedures.

Rather than use an approach that relies on an open-ended definition of homologous use, such as the one contained in the proposed regulation, the AATB recommends that the FDA devise new criteria that better accommodate current surgical and tissue banking practices.

This would speak to the level and nature of the risk to patients. These criteria could be developed specifically for non-viable structural bone tissues. We recommend that these criteria recognize that bone implants should be considered and recognized as tissue when used for the same basic characteristics, not functions, that they have inherently, regardless of the anatomical site from which they were recovered or the site in which they are implanted. The same approach to developing workable criteria should be taken with other major tissues as needed.

The AATB finds the FDA's proposed minimal manipulation for bony non-viable structural issues to be as problematic as the proposed homologous use criterion. The FDA's criteria as currently defined could lead to the

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widespread classification of regulation of many currently available allografts as medical devices.

The reasons for this classification would have nothing to do with the potential risk to patients. All criteria should be predictable and easily understood by anyone covered by the regulation. This is not the case with the proposed criterion for minimal manipulation.

We anticipate that this criterion could be very difficult to apply in a consistent and unbiased manner. It could also be the source of considerable controversy and legal challenge.

The AATB is not aware of incidents that would lead surgeons, the FDA, or other knowledgeable observers to conclude that there are currently types of bone tissue processing that present risk to patients. We are also not aware of any approved tissue processing technology that warrants the imposition of additional regulatory controls.

These comments reflect the AATB's deep concern about the working criteria that the FDA has developed to distinguish tissues from products that may have more comprehensive and costly regulation.

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In expressing our views, we do not retreat from our general posture of support for the FDA's efforts to assure the safety and quality of tissues provided to surgeons and patients, goals that have inspired us since our inception.

We recognize the challenges facing the FDA as it seeks to implement a regulatory approach that calibrates regulatory burdens to public health risks. We know that these issues are not easily resolved, and we commend the agency and the Human Tissue and CDRH staffs for their efforts to find solutions.

We ask the FDA to recognize the potentially grave impact that homologous use and minimal manipulation criteria could have on surgical practice, tissue banking, and ultimately on patient care. The fundamental question I think for all of us is whether these criteria will improve the availability, the safety, the effectiveness, or the quality of human tissue for transplantation.

More importantly, will these criteria enhance patient care? We think not. We are concerned that we may be facing a violation of our most fundamental principle, "First, do no harm."

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We urge the FDA therefore to implement the registration requirement, but not the homologous use and minimal manipulation criteria. We are convinced that the FDA has the legal authority to publish a final registration regulation without this criteria.

We thank the FDA for the opportunity to present this information in person, and we are available to answer any questions.

Thank you.

DR. WITTEN: Thank you.

Our next speaker is Dr. Randal Mills from Regeneration Technologies, Inc.

Regeneration Technologies, Inc.

Proposed Regulations of Bone Allograft

DR. MILLS: Good afternoon. My name is Dr. Randal Mills, and I am here today on behalf of Regeneration Technologies, who has also provided my funding for attendance here today.

We have already heard some excellent presentations and very relevant points made, so I will try to keep my comments brief.

Today, I would like to speak on three specific

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issues of tissue regulation, the first being the outstanding safety record of human tissue in transplantation. The second is the uniqueness of this very precious resource, and lastly, our position on the future regulation of human tissue.

First, I would like to take just a minute and describe a little bit about my background and the background of Regeneration Technologies.

Regeneration Technologies is located in Alachua, Florida. RTI was born out of the University of Florida tissue bank in 1998. At that time, it was recognized that the University of Florida lacked the resources necessary to adequately meet the increasing demand for allograft tissues.

It is now the mission of RTI to enhance patient healing and well-being by making available to surgeons the highest quality allograft tissues.

As for myself, I am fortunate to have participated in almost every aspect of tissue banking. I was introduced into tissue banking from the side of donor testing. I established and managed the laboratory at the University of Florida where donor blood was tested for

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infectious disease markers.

Being a small tissue bank at the time, I also had responsibilities that included talking with donor families, including the consent and medical social history process, performing the actual tissue recoveries, and ultimately processing the tissues into final allografts.

I have also worked directly with surgeons to provide them with tissue grafts that are optimized to meet their patients' needs. Throughout these experiences, I have come to appreciate and value the uniqueness of this very precious resource.

Our role in this process is to help facilitate the transfer of this gift from the donor to the recipient.

On tissue safety, human tissues as we have heard repeatedly today have been used safely for decades. The technology underlying their success is not new. Over the past 50 years, the risks associated with tissue transplantation have been well defined, and to address these risks, tissue banks and regulatory agencies, such as the FDA, have instituted responsible standards that

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ensure the safety of the tissue supply today.

Regeneration Technologies strongly supports and adheres to these measures. In addition, RTI has developed and adheres to standards that exceed these standards set by FDA or other state or other regulatory agencies to include mechanical testing and testing for biological properties of our allografts.

Because of the excellent safety record of human tissue and because of the substantial benefits that allografts provide to the recipients, the demand for these grafts has increased. This demand has resulted in a shortage of certain tissues. It is important to remember that the significant benefits realized by the recipients, coupled with this outstanding safety record, is what has created this demand.

Human tissues are also very unique. Allografts, when used in transplantation, offer tremendous benefits that are unique only to human tissue. This is most evident by how the body responds to this tissue.

Transplanted bone, once implanted, is not rejected, but instead incorporated and remodeled over time. The recipient's body transforms the graft into

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cell. These properties are unique to human tissue and allay many of the concerns encountered with devices.

Allografts are also unique in how they are obtained. Donor tissues are a gift from the donor to the recipient. Tissues are not like devices. The supply of tissue is not controllable. When the demand increases, we cannot simply order more.

Tissue establishments, therefore, have an obligation also to the donor family to ensure that precious gifts that were offered are used to provide the maximum benefit to the recipients.

We are concerned that the classification of tissues as devices may interrupt this transfer. Additionally, we are concerned that additional regulation would have a negative impact on the donation process and possibly lead to an even larger unmet demand.

Allografts are not like devices, and we must consider allograft of the potential effects when enacting further regulation.

On the future of tissue regulation, RTI supports any additional regulation that is necessary to mitigate a public health risk. We do not believe that there

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currently exists a risk that requires further regulation for tissues that are currently available to surgeons. However, it is recognized that in the future, tissue-based technologies may expand into areas where additional regulation is warranted.

Such additional regulation should reflect and mitigate these risks associated with new technology.

We do not believe that the proposed approach as written is feasible. Specifically, FDA proposed a tiered approach where regulation would be proportional to risk, however, we are not aware of any necessary increase in risk associated with the terms "minimal manipulation" or "non-homologous use."

We do think the approach can be amended into a workable regulation that accomplishes the goals of protecting public health while not limiting the supply of allograft tissues or stifling innovation that ultimately benefits the recipients.

To this end, RTI offers the following augmentation to the approach. For tissues deemed either to be more than minimally manipulated or intended for a non-homologous use, a standardized risk assessment would

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be performed. Clearly, the production and standardization of this assessment would need to be one that was created between industry and FDA.

This assessment could evaluate all of the relevant factors of risk including source testing, intended use, sterilization, processing, and others. This analysis would then provide an overall estimate of the risk of the graft.

Based on the results of this type of analysis, it would then be determined if existing or additional process controls are sufficient to adequately address recipient safety.

If it is found that a significant new risk may exist, additional regulation or adherence to standards may be required. We believe that this addition to the approach would account for those tissues that may be processed in a way that would deem them more than minimally manipulated, yet carry no additional risk.

Additionally, this type of assessment would allow a processor to employ the most meaningful controls to ensure tissue safety.

In conclusion, I would like to stress two key

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points. First, the use of tissue in transplantation has improved the quality of life for millions of patients while maintaining a sterling safety record.

Secondly, human tissue is different from traditional medical devices, and these differences must be considered when enacting any future regulation. Additional regulation is only necessary when new risks are defined beyond those associated with current technology.

RTI thanks the FDA for the opportunity to comment on this very important issue, and we look forward to working with the agency in developing meaningful and reasonable regulation. We hope the agency will consider the addition to the proposed approach that we have submitted, and we intend to submit a detailed version of this approach in written form during the comment period for this meeting.

Thank you.

DR. WITTEN: Thank you very much.

Our next speaker is Mr. Frank Glowezewskie from the University of Florida Tissue Bank.

University of Florida Tissue Bank

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History of Minimally Manipulated Allograft Tissue

MR. GLOWEZEWSKIE: As stated, my name is Frank Glowezewskie. I am representing the University of Florida Tissue Bank today, the reasons being that I have been on the faculty there now for the last 30 years, just retiring, was also the founder of the tissue bank, long-standing chairman of the board now retired, and currently, the Director of International Education for both UFTB and RTI.

I would like to thank the panel for the opportunity of addressing everyone today. I had originally outlined this talk to be given in script form for clarity, but at noontime I committed a capital sin and went ahead and changed my talk to try to cut out as much as I could that would sound redundant. So, please bear with me if I hit and miss a little bit.

[Pause.]

If there is problems, I can do it without the slides.

While they are trying to figure this out, the University of Florida tissue bank was founded in 1982 for human usage. However, I was there for 10 years prior to

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that, and we conducted extensive research into tissue banking to tissue application to assure the efficacy of this science without our own institution, and obviously, through sending materials out to the rest of the nation and at times to other parts of the world, so we have a fairly extensive background, my own personal 38 years in the tissue industry and the University of Florida predating me by quite a bit in their studies.

DR. WITTEN: Also, can you just state for the record who is paying your way?

MR. GLOWEZEWSKIE: Yes, ma'am, the University of Florida tissue bank.

DR. WITTEN: Thank you.

Maybe I will take this opportunity to ask the panel, those people who have spoken so far, and plus anybody else, a question, which I was going to save later for the questions from FDA panel time.

That is, there has been a lot of discussions about risks, that is, that these are low-risk products, there is a long history of use without risks, and I am interested to know currently how risks would be reported and what your recommendation would be regarding the kinds

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of risks that would need to be reported.

For example, currently, if the surgeon experiences bone graft collapse of a given product, would they report it back to a tissue bank or what would happen with that information? So, I will throw that open particularly to the physicians on the panel, but to anybody else who would like to comment.

DR. JAFFE: The complications of allograft are usually infection or graft failure. There are so many variables that go into it, and what is alluded to as surgeon technique, as well.

We at the present time do not have a mechanism to follow allografts or to report the complications because it is so multifactorial.

DR. WITTEN: I guess I have a follow-on question, which is there certainly were some information provided by at least one of the speakers, I think Dr. Laurencin, and also it has been noted by other speakers that different types of processing can result in altered mechanical or bioactivity characteristics.

I guess one question I would have for the surgeons is how would the surgeons know about how the

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performance of the particular product they are using might or might not have been altered by the processing of that particular product if there isn't this kind of systemic reporting.

DR. LAURENCIN: I think just as Dr. Jaffe said, it is very difficult to be able to analyze why the graft may fail. I think that is why it is more important to at least characterize the graft tissue before it goes out, when there is a good handle in terms of what the mechanical properties are, what the biological performance of the graft is.

Even if one has a failure, I think one can feel fairly confident that the failure isn't due to the graft material, it is maybe due to the other factors.

DR. WITTEN: Thank you.

DR. JAFFE: One of the problems that we have is to try to educate our own users. Oftentimes grafts are used or asked to perform roles in which they weren't intended. They are put into certain host beds in which there is compromise to the tissue, so the grafts can't function and do their normal activity. This is in situations that may have previously been irradiated or

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have previous infections, and we are asking the graft to perform a biological activity in which the normal host factors can't go through the usual process.

So, I think surgeon education as to some of these processes is important, as well as the surgeon understanding and identifying the roles that the grafts are supposed to be used in.

DR. WITTEN: Thank you.

I think now we can move on to our speaker.

MR. GLOWEZEWSKIE: Sorry for the delay, but there was some kind of disk problem.

The first slide, if you would.

Keeping within the bounds of the FDA's proposed or final rule, as depicted, for minimal manipulation, it states that, "The cutting, grinding, and shaping of a tissue which does not alter the original relevant characteristics of the tissue, that relates to the tissue's utility for reconstruction, repair, or replacement," in keeping with this, I would like to offer just a short review of minimal manipulation with the caveat that at the end of this, and through the research of it, it seems like there is very little evidence for

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the regulation within the tissue industry.

However, in accordance with the rule from the FDA, the application of minimal manipulation in tissue banking by no means is a recent innovation, as you have heard many times today, reliable -- and I underscore reliable -- publications addressing these or this cuttings or the shapings, grindings, and transplantation of both the autograft and allograft tissue dates back, to a minimum, of the 18th century.

A myriad of people have been involved in these endeavors and they are just too numerous to mention or to report today, but I have singled out some. They really need to be recognized and their milestones appreciated.

People such as Macewen, Senn, Dr. Cloward and Inclan have really contributed so much to the tissue industry over the years, the years being 120, as previously mentioned.

If we look at the slide, we can appreciate some of those dates dating back to Macewen, who was reported to have performed the first successful allograft procedure under aseptic conditions in 1878, moving up to Senn in 1889, and even more forward, to Inclan, Dr.

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Cloward, who we will speak about later.

So, there is quite a history of success and research into the art of tissue banking and transplantation.

A striking commonality among these efforts is that each person, and not only through the removal of the graft material, which incidently is minimally manipulating that material, but not only through the removal, they have employed other forms of minimal manipulation to the tissues prior to their storage and/or their transplantation.

Also worth noting is that following these cuttings and grindings and different forms of shaping, each of these various tissues have retained their relevant reconstructive and/or biologic characteristics.

Now, coupled with the difficulties associated with the collecting of these tissues was the added disadvantage of manipulating them within the operating theater. Again, that also extends to after manipulating them, how do you store them, and what steps are necessary to keep them until transplantation.

These efforts soon turned towards these

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functions being performed in, and more importantly, quality controlled through, various tissue banks. These efforts really began in the late 1800s, and they expanded the different types of manipulated tissues available to increase the various options that the surgeon and the patient had for treating of their pathology.

Throughout these efforts, attentions were focused on the safety while expanding the variety of modalities of treatment that we could offer the patients.

I pause again I want to focus back on the safety. As mentioned numerous times today, as the industry exists today, there are no reported safety issues. We have a sterling record within the tissue industry, and I have no reason to think that that will change through our current configuration and association affiliations.

If you look at FDA's language on demineralized bone matrix, if you feel like writing, that's in the Federal Registry, Volume 63, No. 93, Thursday, May 14th, 1998, Propose Rules to Minimal Manipulation, paragraph 4.

There tissues are, "used for homologous function and is not combined with a non-cellular or non-tissue

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component that is a drug or a device." Therefore, all these tissues that we are speaking about fit within that category of being minimally manipulated.

Rick and others have said it, and I will say it again. Bone is bone, and if you want to extend that to homologous use, the skeleton is the skeleton, as the skin is the skin. So, wherever bone is transferred from one portion of the skeleton to the other, should fall under minimally manipulated tissue for homologous use.

Now the earliest date that these reconstructive or replacement tissues were introduced for repair in the spine is really anybody's guess. I mean we can go back to Cosmos and Damien as many people do several hundred years following Christ, but we do know from the literature that Cavner introduced this concept as early as 1931.

Picking up on his research and endeavors, Speed successfully demonstrated these procedures of utilizing allogeneic bone and spinal fusions, and reported on his success in 1938.

The literature also documents that Dr. Cloward, Smith Robinson, continued to popularize these various

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techniques and procedures all the way through the 1950s. On the screen is a partial list of some of these and their innovations, but if you notice on that list, Dr. Vich is mentioned. Dr. Vich was one of the first to report of his threading of cancellous bone dowels in the actual operating theater, but as pointed out, this has many drawbacks - the wasting of a surgeon's time, the prolonged time in anesthesia in the operating room for the patient, the extra morbidity because of the wound being open, and so on.

So, once again, these efforts were quickly transferred to the vicinity of tissue banks.

Now, the rectangle chips, dowels, sticks, different shapes, step-cut tissues were once again only minimally manipulated to allow them to fulfill their structural biological and/or physiological function to achieve successful skeletal repair, from the skeleton to the skeleton.

Vich once again described this technique of cutting threads which we see an being minimally manipulated, and cancellous dowels in 1985. Today, there is a counterpart to this, and these are the cortical

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threaded dowels which are used today in literally tens of thousands of patients once again with reported minimal or no complications.

We have heard a lot of numbers today, too, and I keep trying to pick up through the literature the exact number, but with the 250,000 total tissue grafts being performed in the neurologic community alone, when you consider orthopedics, oral maxillofacial, periodontal plastics and reconstructive application worldwide, this is literally millions of grafts a year that are going into human beings with no or very few complications and/or problems, and again, back to the 1800s.

The key issue concerning these tissue grafts is that they have all been minimally -- boy, this is tough to say three times -- minimally manipulated in some manner or another. However, through these various steps, once again, of the cutting, of the shaping, of the notching, of the threading, of the grinding, of the demineralization, and equally as important, of the preservation, packaging for preservation, this basic physiologic, biologic structural function of these materials has not been changed.

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We have heard today of reported 98.5 percent success rate. The literature is full of greater than 90 percent and greater than 95 percent success rates reported in different clinical studies.

So, once again, with these success rates, it would seem there really is no clinical red flags put up as to the safety of these tissues, that their normal revascularization, resorption, repair, incorporation, these processes remain the same, thereby showing that the tissues have not been altered in any way other than possibly shape.

The FDA, as you know, and the reason we are here today, has taken regulatory action concerning tissue over the past several years. These regulatory actions or these regulations have applied mainly to the screen and the proper testing of donors, as well as to good recordkeeping.

I personally believe, and so does the University of Florida Tissue Bank, and I believe most of us here, that these steps were well warranted and that they have added to the safety of the tissues that we use in this country today and throughout the entire tissue industry.

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With these regulations in mind, however, and the history of the utilization of minimally manipulated tissues supplied through tissue banks, there has been shown no significant health care issues and/or risk.

So, if imposed, new regulations singling out individual tissues would seem to have a far-reaching implication on not only patient care, but on the entire tissue industry and the various tissue banks, and this is not even to mention the increased cost in the providing of these tissues, that has to be passed on through the health care system.

So, in summary, from these and other facts and evidences that we have heard today, it would seem to suggest that these materials should remain in their current status as tissues, and continue to be viewed as they are in reality, as unique and separate from devices.

We would further -- and "we" again being the University of Florida and myself -- we would further submit that the threaded cortical dowel, as well as all other bone and connective soft tissues, that are minimally manipulated, meet the definition proposed by the FDA, and that no individual tissue or groups of

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tissues be singled out.

Therefore, it is our belief that no further regulation within the tissue industry is warranted at this time.

Thank you.

DR. WITTEN: Thank you, Mr. Glowezewskie.

Our next speaker is Daniel Mans from Sulzer-Spine Tech.

Sulzer-Spine Tech

MR. MANS: Thank you, Dr. Witten. Good afternoon. My name is Dan Mans, and I am the Vice President of Regulatory and Clinical Affairs for Sulzer-Spine Tech, who has paid the costs of my travel to this session.

I would like to thank the FDA for this opportunity to express the views of our company in this public forum.

Sulzer-Spine Tech manufactures medical devices that are used in patients in need of spinal fusion surgery.

Currently, our company does not procure, process, or distribute human tissues for use in medical procedures.

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Historically, our company has been perceived as an advocate for increased regulation of allograft bone, however, it is the position of Sulzer-Spine Tech that regulation of human allograft bone as a medical device is not in the best interests of the public health for the reasons already outlined by several of today's speakers including Drs. Kitchel and Fessler.

We do feel it is important to make a distinction between allograft bone and those products created from elements of allograft bone that also consist of materials, such as metal, polymers, or animal tissues. The FDA's treatment of these products as medical devices is appropriate from our perspective.

As for minimal manipulation and homologous use, Spine Tech applaud the FDA's efforts to develop a mechanism by which tissue products can be distinguished from medical devices, but agrees with many of the presenters today who have expressed concern that these definitions are vague and that they will be difficult to apply uniformly and fairly.

Ultimately, we find the statements expressed this morning by AdvaMed on this matter to be persuasive,

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and so agree its position. However, recognizing the specific requests made by the agency in preparation for this meeting, we provide the following interpretation of minimal manipulation as it relates to human allograft bone used for spinal reconstruction and repair.

We suggest that any process which does not alter the essential microstructural elements of allograft, that is, specifically the collagenous and mineral elements, are processes of minimal manipulation.

Specifically, these include, but are not necessarily limited to, the cleaning, cutting, shaping, and forming of allograft bone.

Thank you for consideration of these comments.

DR. WITTEN: Thank you very much.

Our last speaker for this session is Jennifer Davis from Hyman, Phelps & McNamara.

Hyman, Phelps & McNamara

Legal Issues Posed by the Proposed Tissue Regulations

MS. DAVIS: Good afternoon. My name is Jennifer Davis. I am an attorney with the Washington, D.C. law firm of Hyman, Phelps & McNamara, where we have been closely following the development of FDA's proposed

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scheme for regulation of human tissue-based products.

I am here today at the request of Regeneration Technologies. The goal of this presentation is to point out some of the specific legal issues that we perceive to be raised by FDA's proposed framework from the perspective of bone allograft processors, and hopefully to suggest some approaches that the agency might take to address these issues.

I was pleased to see this morning from FDA's presentations that they really are here to listen. I think there have been a lot of good comments presented, and I would hope that they would take those to heart.

The first issues concerns what a lot of other people have touched on, and I am going to try to present it from a different perspective - the vagueness of the minimal manipulation and homologous use criteria.

We think that this raises at least two legal issues, one concerning the adequacy of the public notice that is afforded by FDA's proposals at this time, and the other concerning whether the current definitions of these terms would be adequate to guarantee regulated subjects constitutional due process if they were finalized.

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To participate meaningfully in the notice and comment rulemaking process, which is required by the Administrative Procedures Act, interested parties must have from the agency's proposal fair notice of the basis and meaning of that proposal.

We feel that FDA's proposed criteria, minimal manipulation and homologous use, in particular, appear to fall short of this requirement. Some of the questions asked this morning about clarification of these criteria are representative of our view on this.

According to the proposal, however, meeting or not meeting the criteria will in most cases mean the difference between premarket approval requirements and no premarket approval requirements, and this is a significant regulatory consequence.

Only with additional specificity and examples can tissue processors and other interested parties really appreciate how those proposed criteria, as the agency interprets and intends to apply those terms, will affect particular tissue-based products and thereby offer meaningful comments.

Therefore, we believe that if FDA intends to

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promulgate the minimal manipulation and homologous use criteria as regulations, final regulations, the agency should re-propose them with more specificity and examples of the kinds of processing and uses that the agency believes these terms to encompass, possibly based on the input provided, for example, by written comments and some of the input offered here today.

A second issue involving vagueness has to do with whether the current definitions would provide processors with constitutional due process. Due process standards require that federal laws and regulations provide regulated subjects with fair notice and a reasonable degree of certainty as to what is required for compliance.

Federal laws and regulations must also provide clear standards to regulators in order to prevent arbitrary and subjective enforcement. As presently formulated, we perceive the proposed minimal manipulation and homologous use requirements to afford FDA virtually unlimited discretion to decide on an ad hoc basis what falls within and outside of these categories.

One ostensible solution to the vagueness of the

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minimal manipulation and homologous use criteria that FDA has offered in its proposal is to caution tissue processors to consult the agency with respect to those products for which they are uncertain.

Setting aside for the moment issues concerning FDA's Tissue Reference Group, that solution consult the agency would really only be tenable if the criteria and the procedures, FDA's procedures for interpreting and applying those criteria are reasonably clear to begin with.

If they are not, then, one can imagine the situation in which tissue processors will feel compelled to seek an opinion on virtually every product that they intend to develop and distribute.

One can envision this undesirable result by taking a look at what happened last year with FDA's effort to classify bone dowels. Prior to that meeting, as others have mentioned, FDA had stated in the 1998 proposed rule, Establishment, Registration, and Listing, that minimal manipulation included the very processes that processors use to create their allografts, for example, cutting, grinding, shaping, soaking in an

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antibiotic solution, sterilization, freezing, lyophilization.

The agency also stated, for example, that homologous use of a structural tissue would include such things as bone allograft obtained from a long bone, but used in a vertebra.

Based on these statements, processors of bone dowels concluded that FDA considered their bone dowels to be minimally manipulated and homologous, and therefore subject to regulation as tissue as opposed to regulation as devices.

Until FDA announced the panel meeting to classify bone dowels, it did not occur to most processors that there was any need to consult the agency regarding the regulatory status of these products.

This brings me to another legal issue concerning the role and authority of the Tissue Reference Group and the procedures employed by that group to perform its appointed functions.

The TRG is only briefly mentioned in FDA's 1997 document, "A Proposed Approach to the Regulation of Tissue-Based Products." Strangely, this group and its

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functions are not discussed or even mentioned in the 1998 proposed rule or the 1999 Donor Suitability and Testing proposed rule.

The agency offered a little bit more information about the Tissue Reference Group this morning, and I think that that is a good start, that there should be more transparency in the TRG's processes and functions.

According to their Manual of Standard Operating Procedures and Policies, this group was established to serve as a single reference point for product-specific questions concerning jurisdiction, policy and regulations.

The 1998 annual report indicates that the TRG has authority to make recommendations regarding entire classes of products. To date, the TRG has issued as least 12 recommendations of which we are aware regarding how new tissue products should be regulated.

It is clear even from the limited descriptions of these recommendations that were made publicly available that they were dependent on the group's interpretation and application of the proposed risk-based criteria, minimal manipulation and homologous use.

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Making jurisdictional recommendations based on the risk-based criteria, we think is a rather significant regulatory responsibility with important consequences, but it is not described for public consideration and comment in FDA's rulemaking proceeding.

We had mentioned this morning of the request for designation regulations in Part 3 of the agency's regulations. Those were promulgated through notice and comment rule making. Even they do not authorize the ombudsman to make jurisdictional decisions with respect to entire classes of products.

Another issue I would like to talk about is the secrecy with which the TRG's recommendations appear to be made. If tissue processing entities are going to be expected and recommended to consult with the agency, consulting the status of their products, it seems there should be greater transparency in the TRG's procedures and methods, as well as in the results of its evaluations.

Failure to make more information about the TRG's evaluations publicly available could conceivably result in repetitive review of similarly situated products. It

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could also result in uneven decision making, which is actually a result the TRG was established to prevent.

These outcomes would be minimized, we believe, by establishing public precedence that the industry can look to and rely on.

A final question about the TRG concerns the legal nature of its recommendations and responses to product jurisdiction questions. I think someone mentioned this morning that it was issuing only recommendations, and not decisions. Presumably, these recommendations would not have the same regulatory status as a response to request for designation, but it is really not clear how they operate to bind the agency - would they bind the agency like an advisory opinion?

As we understand, for example, the classification panel meeting scheduled for last year and then canceled was the direct product of a recommendation by the TRG. It seems to be a pretty significant influence for this group.

One final issue I would like to address, and others have touched on this, is whether than minimal manipulation and non-homologous use conclusions, using

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these definitions, would be a sufficient basis on which to require premarket review.

FDA has stated that the purpose of these proposed risk-based criteria are to address factors that bear on the safety and efficacy of tissue-based products. A product's risk is perceived to be greater under the proposal if the product is more than minimally manipulated or promoted for a non-homologous use.

As the written comments submitted to FDA and the presentations earlier indicate, there is a long history of safe and effective use of bone allografts in the spine to restore stability and function to the spinal column.

The history is documented in the medical literature, as well as by the surgeons who use these allografts on a regular basis. Moreover, the medical and scientific communities' understanding of the term "homologous" appears to be quite different from the more narrow perspective that FDA seems to be advancing.

FDA has also suggested with respect to its minimal manipulation criterion that it's a moving target in the sense that processing which may be at first considered more than minimal manipulation, may later come

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to be understood as minimal manipulation based on experience and understanding of the technique.

Well, this may ultimately serve a goal of less regulation and proportional regulation. It could also lead to uneven treatment of similarly situated products, actually punishing innovation or penalizing innovation by calling the first product on the market more than minimally manipulated and requiring premarket review, while allowing others to come into the market more easily based on a later finding of less than minimal manipulation.

Various types of bone allografts have been used safely and successfully in the spine for decades, long before the enactment of the 1976 Medical Device Amendments. For more than 20 years after the Medical Device Amendments were enacted, FDA did not make any attempt to regulate most of these tissue allografts as devices.

We don't perceive or understand the justification now for FDA to regulate these articles as devices. As others have mentioned, and we agree, we are not aware of any major new public health threat.

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FDA has already promulgated regulations to address disease transmission concerns, and those appear to be working quite well. Further, other organizations, such as the Tissue Engineered Medical Product Standards Group of the American Society of Testing Materials, are presently addressing standards that will appear to deal with aspects other than disease transmission, such as those the agency has been asking questions about this morning.

The standards may well address the outstanding concerns, and we feel that perhaps it is too early to move forward with more burdensome regulation until we see what the product of these standards-making initiatives is.

Even if FDA were to conclude under the current formulations of its definitions that certain allografts used in the spine are more than minimally manipulated or used for non-homologous purposes, we don't feel that this means premarket review is necessary to ensure their safety and efficacy.

If the stated goal of FDA's proposed approach is to avoid unnecessary regulation and burdensome

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regulation, requiring premarket review of allografts, whose history has already been documented for many years, would seem contrary to this goal.

One example that is rather poignant is when FDA attempted or made efforts to require premarket submissions for heart valve allografts, the continued availability of the allografts was severely threatened although FDA eventually stipulated in a lawsuit brought by the processors that it would not require premarket submissions, HVAs today, heart valve allografts are still regulated as devices. The agency has proposed to regulate them as tissue without any requirement for premarket submission or review.

If the agency were to require the same type of review for bone allografts, like HVAs, the continued availability of bone allografts may also be threatened.

In conclusion, FDA's proposed framework appears to raise important legal issues concerning, among other things, the authority and functions of the Tissue Reference Group, and the definitions, interpretations, and applications of the proposed risk-based criteria.

With respect to how the agency might achieve

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more clarity in its minimal manipulation and homologous use criteria, we believe that FDA should re-propose the definitions with more specificity and examples of the types of processing and uses that the agency believes these terms to encompass based on input provided through public comment and also through the presentations here today and at other public meetings or workshops which FDA might convene to offer an opportunity for a more focused interactive dialogue between the people affected.

As for the Tissue Reference Group's significant role in determining how various types of tissue-based products will be regulated, it appears that the agency has an obligation to describe this group's role, authority, functions, processes, and its recommendation's process, as well as the public availability of these recommendations in the proposed rulemaking in order to comply with the notice and comment requirements under the Administrative Procedures Act.

FDA should also endeavor to make more information about the TRG's recommendations available to the public. Establishment of the public precedence will help, in our view, to reduce repetitive review of

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similarly situated products, as well as promote consistent regulatory treatment.

In closing, I appreciate the opportunity to present these views today, and I an encouraged by the agency's willingness, as it mentioned earlier today, to listen and really take to heart what has been said here.

Thank you.

DR. WITTEN: I would like to thank our last speaker and ask the FDA Panel to come up to the podium here.

Questions from FDA Panel

Now, I would like to start on the FDA questions.

Would anyone like to start?

[No response.]

DR. WITTEN: Perhaps I will kick off the questions then. I will just ask in particular Dr. Laurencin, but anyone else on the panel who would like to answer, which is there has been a lot of discussion about what type of standards would be desirable, and Dr. Laurencin in particular, it seems you have put a lot of thought into it, as is obvious from your presentation, and I am interested to know how you all would see those

standards used, that is, would you see those standards used a characterizing as the product on the labels, so the surgeons could then look at the mechanical characteristics and biological activity, and select a product according to his needs or what?

DR. LAURENCIN: Well, just looking at biological performance, I think that it be important to be able to compare -- there is really now a plethora of different processed products that are actually on the market, and it would be very useful to be able to examine those products to be able to ensure that the biological activity is uniform throughout for what differences there are.

I think in terms of mechanical properties, it gets quite important in terms of the applications that are going to be used. There is really again a plethora of applications that will be there.

So, my feeling would be, number one, in terms of biological properties, very useful to standardize what the biological assays are for determining whether it is going to be histomorphometric activities or an in vivo, non-union model, et cetera, and I think in the industry

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there are no uniform ways throughout in terms of determining it. I think that would be number one.

In terms of mechanical properties, depending upon the type of graft material in the application, I think it can be very important in terms of making that determination, in terms of mechanical performance.

DR. WITTEN: Thank you. Any other questions? Dr. Feigal.

DR. FEIGAL: If you look at the devices that have the least amount of regulation, those are the Class I exempt devices, which are exempt from premarket review, so you can say, well, what is left in terms of quality controls for those kinds of products.

One part of it which has been discussed today, and not very much opposition, has been registration and listing, so you can identify the universe, but one of the requirements that I would be curious to have some comments on, both from the practitioner side and from the banking side, the other side is to have a system of identifying problems.

Some of those would be in the category of manufacturing errors and accidents, others would be

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product problems that occur after release and what the corrective actions are, and that type of thing.

It is those types of systems that are still expected to be in place and some of them lead to reporting requirements to the FDA.

With the current system -- here is my question -- with the current system, how good do you think these types of error detection, reporting feedback loops, corrective kinds of actions are within this industry? Is this an area where, in the absence of regulation, such systems have developed, and is this an area where there are any concerns?

DR. FESSLER: We have a system of peer review and publication. I think that this has already developed in that part of my job as an academician is to test everybody's product and to see how it works.

We do that in animals before we do it in humans, and then we do it in humans, and then I talk to my peers at national conferences, at international conference, and in the hallways, and I publish those results, so I think we have a very accurate mechanism to detect success and failure among all of these products right now.

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DR. WITTEN: Does anyone from industry also want to take a stab at answering this?

DR. MILLS: I think one of the key concepts you bring up is how do you address the quality system issue in tissue industry. I will just tell you from RTI's standpoint how we did it.

RTI voluntarily subjected itself to inspection and eventually received ISO 9001 certification, and because of that, RTI is already obligated to implement quality systems. We are required to have feedback loops. We are required to do design control, to do risk assessments, and have established a complaint file system and a corrective action system.

I can tell you from personal experience internally, those systems work very well in controlling and improving the quality of the grafts that we are able to provide to surgeons.

MR. RUSSO: Richard Russo for AATB.

Two comments. First of all, there is a regulation now currently in force, 1270.31D, which says that there shall be procedures during processing for the prevention of cross-contamination or contamination, that

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are written, validated, and followed, and this is the basis right now of inspections of tissue banks by the FDA inspectors locally.

So, there is a basis for this issue of procedures. On a different note, I will comment that the differences between a graft like bone, that is remodeled, you know, resorbed by the body, but remodeled, not just absorbed like a synthetic material, introduces issues, such as the patient's health, the conditions of the bone graft site, and the surgical technique in addition to the basic structural integrity of the graft, so it becomes very difficult, as was pointed out, from a biological or biomechanical perspective, to look at this and simply report a problem.

But certainly there can be, and it has been suggested, that problem reporting occur. It is already being done on a disease transmission basis at this point in time, but not on a performance basis.

DR. WITTEN: Thank you.

Other questions? Areta Kupchyk.

MS. KUPCHYK: I have a comment and a question, I believe for Dr. Fessler and Dr. Russo.

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Dr. Fessler, when you were speaking, you had mentioned in your presentation that there is 100 percent compliance of tissue banks of the standards that are out by AATB, I believe you were referring to, and I believe that you cited a 1999 FDA notice of the Donor Suitability Tissue proposed reg.

The way it was presented, it sounded as though you were saying that all tissue banks are in compliance, and the way that it had been presented in the notice was that all tissue banks that are members of AATB are in compliance.

I just wanted to make that note, and then to follow up with either a question to you or to Dr. Russo, how many tissue banks are not members of AATB, and do you have any sense of how many banks are out there and what standards they might be following, if not yours?

DR. FESSLER: I don't know the answer to that.

MR. RUSSO: Responding to the question about the number of tissue banks, we don't have an actual count. We know that there are 28 accredited tissue banks that process bone tissue -- that process bone tissue. There are more tissue banks that distribute bone tissue or

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recover bone tissue, but there are 28 that actually process that are accredited.

I would presume that there is something on the order of like say another 10 that might be active, that are not accredited, but we don't have an accurate number.

DR. WITTEN: Anyone else want to respond? I can't see who is at the end. Is that Jill Warner?

MS. WARNER: It is Jill Warner from CBER. I have a question for Dr. Fessler and others who have argued that FDA's proposed definition for homologous use is illogical and potentially harmful to the public health.

In particular, I think there was a focus on the location where the allograft is used, and that that would be an inappropriate focus for kicking up the tissue to higher regulation.

However, FDA's proposed rules would apply the additional level of regulation to allografts that are promoted, in other words, advertised or labeled for non-homologous use, not for tissues that are simply used by the surgeon in a non-homologous manner.

I guess my question is, does that distinction make any difference in terms of your analysis of the

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effects of the proposal?

DR. FESSLER: Yes, dramatically. What you do then is you put me in the same position I was in with pedicle screws five years ago, where I know that this is in my patient's best interest, but before I can use it for them, I have to give them an absurd discussion of whether it is approved for use at that particular location.

We know for 50 years that this is the best thing we can do, but now I have to go back and say, well, you know, I have been doing this for 20 years, and we have been doing it for 50 years, and we know this is great, but the FDA doesn't approve it. We are going to create a pedicle screw situation all over again, and I think that is what we are trying to avoid.

What we are saying is we have got the history here, there is no reason to step back and make this harder than it is.

MS. WARNER: Just to comment on that, as well. Certainly, if the tissue were to be regulated in the lower tier regulation, there would be no FDA approval either at that point. I am not sure I completely

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understand the analogy, because the 361 product would not be subject to FDA approval, it would be a legal product

It would also be legal to be used in a manner as the surgeon sees fit.

DR. FESSLER: But it is defining it in a way which obscures that.

MS. WARNER: I have just one more comment on that. I think our concern about if a product is actually promoted or labeled or advertised as being effective in a certain way that isn't its native state, that there be more issues than whether it will work in that manner.

I think I understand your concern that there has been a long history here.

DR. FESSLER: But I would argue that location is not native state. You know, cancellous or cortical bone taken from any part of the body is indistinguishable from cancellous or cortical bone taken from any other part of the body. So, to impose an artificial location definition for homologous doesn't make clinical sense.

MS. WARNER: Thank you.

DR. WILSON: Any more questions?

I think we will stop for a break now. We are a

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little bit early, but we will reconvene at 2:35.

[Recess.]

SESSION IV

Public Discussion/Comments (Continued)

Moderator: Philip Noguchi, M.D., CBER

DR. NOGUCHI: As we move into this last important session of today's meeting, I want to thank everybody for continuing to stay here and the very active participation by everybody involved.

In continuing the previous discussion of our main topics of definitions of minimally manipulated and homologous versus non-homologous use we also have some very important components of the patients who actually receive the benefits of all the work that everybody has been doing.

I am Phil Noguchi, Director of the Division of Cellular and Gene Therapy at FDA, and you all have paid my way here as a member of the public branch of the Executive Service.

I think that is something that you all need to keep in mind, and we will try to make sure that FDA doesn't just remain faceless, but that you have names and

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faces to go along with everything else.

Just once again to say there will be several of the patient advocates here who won't be able to participate directly, but there will be a videotape shortly.

Our first speaker is going to be Mr. John Block from Telos.

Telos

MR. BLOCK: My name is John Block. I am an American who has been living in Europe for the last 12 years and perhaps I can bring a little perspective from outside the United States on the proposed approach.

I am here on behalf of a German company called Telos, who is paying my way. Telos has a deep interest in the proposed approach being discussed today. We have been trying to follow developments in this area in the U.S. as closely as possible.

I have to apologize for the title which has a mistake. It is because I think I am losing my English. The title of my presentation is Moist Moderate Heat, and not Moderate Moist Heat MM Processing System for Homologous Structural Bone Allografts from Surgical

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Donors.

I had some data Tomford in 1995, and today we have seen that the use of allograft bone has doubled. We just heard from the AATB saying that 650,000 allografts were used last year.

The overwhelming majority of allograft bone is cancellous bone, and the primary source of allograft cancellous bone is femoral heads from surgical or living donors, which are living patients undergoing total hip arthroplasty procedures.

My talk will focus principally on these allografts which are typically used as bone void fillers, and forgive me, but I assumed that they are homologous structural function.

I would like to talk about three specific issues, minimal manipulation, discuss two examples with regard to sterilization, disinfection, or viral inactivation of bone allografts, to look at surgical or living donor versus cadaver-sourced bone allografts, and thirdly, the utility of a six-month repeat testing versus viral inactivation processes.

So, it may be more, but this is all I could find

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in the literature from Phillips, in a book called, "Advances in Tissue Banking," Volume 3. Gamma irradiation is currently used by half the American tissue banks.

There appears to be a ritual dose of 25 kGy or lower for microbial inactivation. In fact, the AATB 1998 standards specify a minimum of 15 kGy, but too often there is little allograft-specific process validation based on the size or density of bone or the way they are packed and sent to the sterilizer. I have heard stories of them going in barrels to the sterilizer.

So, we need to see something in the form of kinetics or virus decay. I am looking at the reduction factors of the allografts based on size, density.

In a couple of recent studies, the HIV bioburden inactivation dose in allograft bone has been estimated to be 35 kGy, with a sterility assurance level of 10^{-6}, anywhere from 36 to 89 kGy, and there seems to be a disparity between these estimates and the ritual dose.

If we look at alloplastic bone void fillers, for example, which have no risk of HIV, hepatitis, but they do need to show SALs of 10^{-6} for FDA marketing approval,

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and then Campbell and Lee, in 1999, concluded based on his estimates in bone allografts that gamma irradiation should be disregarded as a significant virus inactivation method for bone allografts.

When I looked at the proposed approach, we see that gamma irradiation sterilization is cited as an example of minimal manipulation, but is it really minimal manipulation for bone allografts when using the doses needed to prevent viral transmission?

I would like to talk about another minimal manipulation technique used in Europe. It is actually a new application of an old technique. It is moist moderate heat treatment of surgical femoral heads, and by "moderate heat," we mean less than 100 degrees centigrade, and there has been more than 60,000 femoral heads treated with this process.

We have been able to show a robust disinfection reduction factor of greater than 8 logs for HIV in some well-known institutions. The clinical osteointegration rates appear to be similar to minimal manipulation, microorganism inactivation methods, such as gamma irradiation, at low exposure levels and ETO

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sterilization.

So, if the FDA is going to include gamma irradiation sterilization without specifying any parameters, then, we would like them to explicitly include moist moderate heat treatment as an example of minimal manipulation of homologous structural surgical bone allografts in its finalized approach.

The second point is surgical or living donor versus cadaver-sourced bone allografts. In the proposed approach, there is no differentiation made as to the source of the bone allografts although the risk profiles are very different.

Surgical thermal head allografts typically come from older living hip patients who have a low risk for virus transmissibility, and we have heard that the most important selection factor, which is screening, these patients are available for thorough and extensive screening, and post-donation follow-up, for example, for CJD.

There is a small, closed loop. By that, I mean the orthopedic surgeon knows who the donor is and knows who the recipient is, and yet, for example, the AATB

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requires repeat blood testing of donor at six months for HIV and hepatitis.

If we look at cadaver bone allografts, it is doubtful there is as thorough an extensive screening procedure, there is no post-donation follow-up. The bone is generally sent out of the hospital, kind of a black box approach, and obviously, there is no repeat blood testing possible at six months.

So, what is the result? We have lower risk bone allografts in terms of microorganism transmissibility, are being held to a higher safety standard than high-risk bone allografts.

So, on the last page of the proposed approach, you will find a proposal for specific communicable disease controls table. We wonder if to even the balance between cadaver bone and surgical bone, it should include that allograft bone from a cadaver multi-organ donor should be held in quarantine until the recipient of a vital organ from the same donor, vital organ being heart, kidney, or liver from the same donors tested at six months for HIV and hepatitis, and that is not done now.

I noticed that the FDA has not addressed

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anaerobic and aerobic bacterial testing, and these issues are not addressed in FDA's final rule, Human Tissue Intended for Transplantation.

The last issue is six-month repeat blood testing versus viral inactivation processes. So, in 1994, in the Lancet, the authors concluded -- which was the Centers for Disease Control -- antibody assays by the FDA may be unable to detect divergent HIV strains. So, is there too much reliance on repeat serological donor testing?

It occurred to me that today we are here to discuss viral safety of bone allografts, but we haven't heard yet from one professor or Ph.D. of virology or a representative from the Centers for Disease Control and Prevention to hear that there is no viral safety threat from a virologist is more reassuring than hearing it from a surgeon.

And where does this end? It seems like with each decade there is more and more testing being required. Are we going to have 20 different serological tests required by the year 2050?

In Europe, we are taking a different approach. By that, I mean the European Association of Tissue Banks

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and the European Association of Musculoskeletal Tissues has stated in their 1997 Common Standards, that HIV-1 and 2, and HCV antibody testing shall be repeated on the living donor at least 180 days following donation and found negative before the tissues can be released into the finished product inventory unless a validated method for viral inactivation, as tested by an independent laboratory is used.

This European proposal has been adopted into German law last year. It is in progress in The Netherlands, Belgium, Canada, and other countries. The benefits of this could be quite interesting. They provide greater safety against unknown, untested viruses and new virus strains.

Let's not forget the world is getting more populated and airplane travel didn't exist 100 years ago. It is possible to perform these viral inactivation procedures with a minimal manipulation of allograft function and performance that will lower the cost of bone banking by reducing quarantine times and reducing rejection rates due to the donors not coming back for repeat testing or secondary contamination.

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So, the FDA is requested to consider the inclusion of a similar clause in its proposed approach, valid only for femoral head allografts from living donors -- I am not talking about cadaver donation -- when an extensive screening procedure and initial viral blood tests have been performed.

This procedure then exceeds the safety measures currently used and advocated by the AATB and FDA for cadaver-sourced allograft bone.

Over the last 10 years, many hospital femoral head bone banks in different countries, including the U.S.A., have been forced to close due to all kinds of requirements even though these allografts have a very low risk for virus transmission.

This centralized approach is leading to more restrictions and higher prices. More recently, new bone banking guidelines and regulations with Germany and Europe taking the lead indicate a trend towards the adoption of a more practical, cost-effective approach to bone banking. Again, surgical bone has been safe.

Specifically, the incorporation and acceptance of the use of validated minimal manipulation viral and

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bacteriological inactivation techniques in lieu of repeat testing could offer a safe method to meet the increasing demand, which has doubled in the last five years, for allograft cancellous bone in coming years.

The need to test for more viruses and microorganisms is growing, not declining. So, for lack of two better words, I think of fine-tuning could be used by the FDA to look again at the proposed approach to reduce the current over-regulation of this low-risk subset of bone allografts, which will continue.

My last observation is that if a company comes to the FDA trying to get PMA approval, for example, for a hand-held gamma irradiation bone sterilizer, first of all, if it needs PMA approval, it needs to show robust viral inactivation, as well as clinical performance in terms of safety and effectiveness of the treated bones, whereas, if a tissue bank sends the bone out to a normal facility which does gamma irradiation, there appears to be little restriction.

Thank you.

DR. NOGUCHI: Thank you, Mr. Block.

Our next speaker will be Victor Frankel, who is

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representing the Musculoskeletal Transplant Foundation.

Musculoskeletal Transplant Foundation

Regulation of Allograft Tissue Forms

DR. FRANKEL: Good afternoon. I would like to thank the FDA for giving me an opportunity to come down here and speak. I am an orthopedic surgeon. I am a Professor of Orthopedic Surgery at New York University, was formerly President of the Hospital for Joint Diseases, a large orthopedic hospital in New York City.

My background in regulation was that in 1962, at the behest of the American Academy of Orthopedic Surgeons, we started the American Society of Testing Materials, F4 Committee on Surgical Implants. I rose to be chairman of that committee.

They did a great deal of work developing standards, volunteer standards, which the ASTM is well known for. In 1974, the FDA was starting to look at an Orthopedic Panel prior to the bill, and I became chairman and organizer of the first Food and Drug Administration Orthopedic Panel and continued in that role for three years.

In 1986, in response to a perceived need for

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much more bone than we are getting from the femoral head, I was a co-founder of the Musculoskeletal Transplant Foundation, so I have kind of seen all sides of this from a using physician, and I have used bone for at least 40 years, 45 years, as a hospital administrator who wants to keep the cost down and make sure everything is safe, to somebody who has been instrumental in starting a large foundation.

Musculoskeletal Transplant Foundation was founded by a group of doctors. It's a not-for-profit foundation. We built an entire budget, monies for orthopedic research every year, and last year, in either money or kind, we put out $1.7 million for orthopedic research.

We have distributed more than a million bottles of bone over the past 13 years, and have not had a single disease transmission. We have a feedback mechanism if something doesn't go right, but the idea of this is to establish to the highest standards in allograft technology and safety, exceed your needs for quality and improvements in tissue recovery, processing, sources, fund grants, fellowships support and extramural research

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to advance the science of allograft, and provide education and resource material for the medical community.

So, we are more than a bond distributor, we try to be an education and research organization.

Now, who are we? These are the academic members, the various institutions and hospitals that belong, they are members of our foundation. Just to point out a few - Mayo Clinic, University of Rochester, University of Missouri, New Jersey Medical School, University of Texas. We are a nationally based organization.

We have a board of directors of people knowledgeable in bone grafting, almost all orthopedic surgeons except for John Sherman, Ph.D., used to be Associate Director of NIH. So, we have -- well, Dr. Enne King, the father of bone grafting recently, and Dr. Gross in Canada, who is a well known expert in this. John William Tomford, who has been mentioned in several talks.

So, this is a board of directors. We control the foundation and set up its aims. We have a wonderful staff and an administration that carries these out.

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We have a medical board consisting of one member from each place, and I don't read the names, I just show you the number of people we have - Cleveland Clinic Foundation, Mayo Clinic, these are more people. So, just to give you some idea of the depth of our bench.

Now, we have members, recovery and distribution members, Rochester Eye and Ear Bank, Southwest Medical Center, Transplantation Society of Michigan, and so on, and we have referring recovery organizations, so we must have our handle on about a third of the bone processed and delivered in the Unites States. So, it is a big organization.

Now, what we do is advance the state of the art. Years ago I would get a femoral shaft if I wanted to do a spine fusion. I would cut sections out of it, and finally, we were able to make our own sections at MTF and later developed another type of section that has less ability to slip out of place, and has better fixation.

So, this is downstream manufacturing or shaping. This is upstream manufacturing. Now, I would rather have this made in a Class 10 clean room than this, that I saw up in the Hospital for Joint Diseases operating room.

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Not only does it take more time, it costs much more money. The patient is exposed, as everybody said before, with the wound open. So, this is a great service to have this already made.

Now, this technique goes back to after World War I. People talk about Dr. Albee. He was a great carpenter. I think his father had been a carpenter and a cabinetmaker, and he brought those tools and technology into the operating room, and he showed in his book all the devices that we see now - pegs, screws, wedges, and so on. He was a very fine machinist. But it takes a lot of time, and there is a lot of risk attached to it.

Now, I would rather see this done at MTF than I would see it done in the operating room. Let me clarify something about discs. An intervertebral disc in an upright human is basically a load-carrying mechanism. It transmits load from the torso down to the legs, vertebra, disc, vertebra, disc.

There is a little motion in there. Now, motion is very profound in something like a snake, that is all over the place. We don't need that motion. Now, as you get older, and, say, you rupture a disc, and a big piece

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of disc is taken out, that area settles down, the joints in the back get out of whack, and many times you have back pain, or alternatively, you have degenerative disc disease because of heavy work or age, the disc dehydrates, and doesn't look like this nice, gelatinous material you see, but it really looks like some blue crab meat in the Chesapeake Bay left out in the sun too long, it's all decayed, so it no longer has a load-carrying function, it can't, so that the vertebrae settle down on each other, becomes painful.

Now, somebody showed today that if you wait long enough, the vertebrae will hook themselves together and self-fuse. That takes many years and many years of a painful back.

So, by going in and doing the fusion with femoral bone or whatever piece you are going to use, you are speeding up the process, you can use this to jack the disc space up again, so that you don't have pressure on the nerves in back. So, this is not an unusual use of a piece of long bone. This has been done forever, and you are not replacing the disc, you are replacing the function of the disc.

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I would abhor the idea of going to the cadaver, taking out a cadaveric disc and sticking it in a patient. That needs a lot of work. Bone grafting has been going on since Dr. Albee.

Now, what do we suggest? I mean most of our statement is in my prepared statement. The FDA is to be commended for looking into the field. We think they should issue Good Tissue Practices depending and developing the ideas of the AATB and ASTM. After all, the Medical Device Act of '76 relied upon 14 years of work from ASTM in developing standards. There was a body of knowledge all ready to go. The same thing is true for bone.

So, in conjunction with the AATB standards, and the ASTM standards, issue GTPs. After that is done, then, revisit the definitions, which we are concerned are kind of vague, subject to different interpretations, and in the end, I think it will be very costly to the medical system and will prevent as much new bone and new ideas getting to the patient as we would wish. So, concentrate on the GTPs.

Thank you.

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DR. NOGUCHI: Thank you very much.

Our next speaker is Dr. Mark Citron who is representing the Orthopedic Surgical Manufacturers Association.

Orthopedic Surgical Manufacturers Association

DR. CITRON: Good afternoon. My name is Mark Citron. I am with Osteotech, but I am representing the Orthopedic Surgical Manufacturers Association today.

The Orthopedic Surgical Manufacturers Association, or OSMA, welcomes this opportunity to respond to FDA's requests for comments by its stakeholders concerning the agency's regulation of human tissue-based products.

OSMA has carefully reviewed FDA's request for comments, and my presentation today represents the compilation of the member companies' views.

OSMA was formed over 45 years ago and has worked cooperatively with the FDA, the American Academy of Orthopedic Surgeons, the American Society for Testing Materials, and other professional medical societies and standards development bodies.

This collaboration has helped to ensure that

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orthopedic medical products are safe, of uniform high quality, and supplied in quantity sufficient to meet national needs.

Association membership currently includes companies who produce over 85 percent of all orthopedic implants intended for clinical use in the United States. These companies provide for advances in technologies and innovations, in products for the surgeons and patients who require them.

These activities also provide a significant number of jobs for these U.S.-based companies through their global distribution systems. OSMA has a strong interest in ensuring the ongoing availability of safe and innovative surgical implants.

Historically, OSMA has focused on products composed of metal, ceramic, and other man-made materials. At the same time, OSMA works closely with the surgical community who have long considered human allograft as both the standard of care and, in many cases, the only method of care.

OSMA members fundamentally believe that the human allograft products currently available to the

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surgeons should not be considered a device for regulatory purposes. We believe that the provisions of the Section 361 of the Public Health Service Act addresses all relevant concerns.

Therefore, Good Tissue Practices and the associated rules with 21 CFR 1270 appear to control for and address all applicable risks. To limit the availability of these clinically necessary materials could adversely affect those very programs which use human allograft in conjunction with OSMA member companies' surgical implants. These implants are regulated as devices.

We shall expand on this point later today, as well as in our written comments that we shall submit for the docket.

OSMA strongly supports FDA's principle of engaging its stakeholders in a dialogue specific to these emerging regulations. We also believe that the measures taken to date by the agency regarding safety of tissue, such as these donor suitability rules, are to be applauded.

While we have endorsed FDA's actions on donor

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suitability requirements to ensure safe supply of tissue, we have strong reservations about certain aspects of FDA's proposed regulatory approach to tissue-based products.

Of greatest concern are what appears to OSMA as FDA's apparent attempts to regulate tissue in a burdensome and non-transparent manner.

OSMA fears that the potential for these regulatory policies by either being poorly constructed, unfairly executed, or both, could drive out good science and diminish FDA's very objectives.

Poor regulatory policy also poses the prospect of adversely affecting innovation with no clear benefit. We will detail our views on these critical points in greater detail later in our comments.

OSMA continues to have significant questions and reservations about the minimal manipulation and homologous use criteria FDA is using to determine whether a particular tissue-based product will be treated as conventional tissues, medical devices, or biological products.

OSMA also believes that the criteria FDA will

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use to make these jurisdictional determinations cannot be judged separately from the process by which the agency will apply the criteria. Therefore OSMA will be providing additional written comments on the lack of procedures and openness by which we see the agency's Tissue Reference Group determining jurisdiction.

OSMA has previously provided written comments to the agency where we said that human bone allograft materials and specifically those human bone products currently used by surgeons for grafting purposes should not be regulated as devices. They should be treated as tissue under Section 361 of the Public Health Service Act.

It may be of value to summarize our perspective on the two laws surrounding tissue regulation and how they relate to today's meeting.

Different sections of the Public Health Service Act govern, in the first case, the control of communicable diseases, and in the second, biological products. These are the two key sections which are termed 361 tissue and 351 tissue. These two sections can be easily confused.

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For 361 tissue, these products are subject to 21 CFR Part 1270 for such critical items as communicable disease, but they are not subject to premarket clearance.

361 tissues are not like Section 351 products, which are subject to device or biologic regulations. Section 351 tissues require licensure as biologics based on, among other items, their potency.

OSMA supports FDA's effort to distinguish between these two areas of regulation. We believe that the agency is correct in obtaining comments from its stakeholders. We trust that this will be the first of several opportunities of rulemaking in this area.

As such, we believe that the FDA's regulatory standards for rulemaking procedures where notice and opportunity for comment will be applied, and these will be used and are to be encouraged.

We urge more public meetings on these critical matters as the agency clarifies its policies in this emerging area of regulation.

OSMA believes FDA's definition of minimal manipulation and homologous use offer imperfect and uncertain guidance for determining what tissue should be

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regulated as devices, drugs, biologics, or tissues.

As we have described in the distinctions between 351 and 361 tissues, any FDA initiative on the regulation of tissue should address those portions of 361 tissue that are relevant. These include processing controls through Good Tissue Practices.

We believe that the development of criteria, such as minimal manipulation and homologous use have no relevance to Good Tissue Practices, and they are impractical at best.

OSMA fears that the rigid application of these definitions will lead to the imposition of inappropriate and burdensome requirements for these conventional tissues that are currently used by clinicians. Thus, products currently accepted by the clinical community as the standard of care may become unavailable to the surgeons and patients who require them, all because of what we see as unneeded and potentially unreasonable regulatory policies.

OSMA has found, therefore, that the current definition for minimal manipulation and homologous use are potentially harmful for the reasons we have stated

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and will speak to later. As such, OSMA would like to suggest an alternative. OSMA strongly believes that the use of allograft bone in any clinically necessary orthopedic procedure as determined by the surgeon represents homologous use regardless of the amount of manipulation of the product.

In addition, and as previously stated, OSMA encourages an ongoing rulemaking process and suggests that such an approach would present a reasonable alternative to the current impractical definitions.

For example, labeling standards, a part of a notice in rulemaking process, would identify permissible claims as part of a class of products. Such a process could also address product composition, physical dimensions or other product description concerns.

OSMA further believes that current FDA concerns specific to this meeting would likely be addressed by FDA's upcoming Good Tissue Practices standards. Most importantly, OSMA supports a sound and rational approach to tissue processing and welcomes the opportunity to work with the agency in bringing out reasoned and accepted standards, such as GTPs.

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It is also important to state that standards currently exist in the form or accreditation requirements from the American Association of Tissue Banks. Additional national standards are actively being developed by such groups as the ASTM under the Tissue Engineered Medical Products Standards Group.

Thus, in the absence of GTPs, OSMA believes enacting regulatory policies at this time would be premature. Further, such actions are disproportionate to the degree of risk. The controls that currently exist are capable of addressing all identified risks, and finally, forcing a regulatory scheme at this time would likely be disruptive to ongoing standard setting initiatives.

We believe such a disruption would be at odds with the agency's own goals to establish standards either voluntarily or under its own GTPs. As FDA applies its proposed criteria and practice, OSMA expects that there will be occasions when the agency and the medical community disagree over whether a specific product has been minimally manipulated or is being put by physicians to homologous use.

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Also, while there may be cases where there is agreement on the application of the criteria, there will be disagreement about the appropriateness of the regulatory requirements imposed.

OSMA believes that such disagreement should be identified and resolved through transparent, open, and early communication between FDA and the medical community. Again, we will provide additional written comments to this point.

To clarify our concerns, an imprecise criteria, such as minimal manipulation and homologous use, generally lead to a lack of uniformity and transparency in regulatory practice. Thus, even if there may be a consensus on how these terms are interpreted at one point in time, the apparent lack of a clear process to adjudicate the decisions would likely lead in the future to inconsistent, unreliable, and unpredictable regulatory opinions.

OSMA is concerned about the prospect of setting a stage for regulatory creep where the implementation of regulatory policies will in the future be either misinterpreted or wrongly applied.

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OSMA believes that there are clear public health benefits in maintaining a safe and continued supply of tissue to the medical community and the patients who require them.

We have found that the current policies and regulations dealing with donor suitability are sufficient to support the continued use of human allograft tissue. As previously noted, unnecessary and overly burdensome regulations in the absence of GTPs is premature and inappropriate to the degree of risk posed by these products.

OSMA finds that such premature regulation is at variance with FDA's stated objectives to streamline government regulation, minimize regulatory burdens, encourage product innovation, and be proportional to the degree of risk the product poses.

We cannot emphasize too greatly our agreement with the agency on a proportional degree of regulation and say that to our knowledge, there have been virtually no reports of infectious disease transmission in the U.S. for processed human bone allografts since 1985, when modern testing methods became available.

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As stated, the imposition of these definitions to regulatory practice is considered arbitrary at best, and would likely disrupt the availability of quality innovative products.

In fact, such action may promote the proliferation of hospital or other intrastate-based suppliers, frustrating the very interests of FDA and OSMA in seeking and maintaining safe and available supplies.

Therefore, a single broad definition where human bone tissue used for repair, replacement, and restoration of function embodies what OSMA believes to be the best alternative to the current proposal.

Thank you very much.

DR. NOGUCHI: Thank you, Dr. Citron.

Our next speaker is Dr. Harvinder Sandhu, who is representing the Hospital for Special Surgery at Cornell University.

Hospital for Special Surgery - Cornell University

DR. SANDHU: An earlier speaker elected not to give my presentation, so I guess I am forced to give it myself. I would like to firstly thank FDA for providing me the time to speak this morning.

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I am an orthopedic spine surgeon at the Hospital for Special Surgery at Cornell Medical Center in New York City. My colleagues and I at my institution have long been advocates of the use of cortical allografts for anterior fusion of the spinal column.

In recent years, we have made extensive use of the precision pre-cut allografts now available for anterior spinal fusion procedures. In our series of patients, we have demonstrated and presented at scientific meeting that such grafts have significantly reduced our operative times, reduced intraoperative blood loss, shortened hospital stays, and shortened the time for our patients to return to work.

For this reason, we were greatly disappointed to learn that regulatory changes now being contemplated by FDA may potentially limit our access to these pre-cut bone grafting materials.

I am here on behalf of myself and my colleagues to advise against regulatory changes that may cause this to occur.

As others have mentioned, and I am going to sound like a broken record, allografts have been used

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along the spinal column for as long as spinal fusion has been performed. Fred Albee, who has been quoted many times today, used allograft bone to fuse a patient with spondylolisthesis as early as 1929.

Reputable physicians in the United States and abroad have long advocated the use of a variety of cut and shaped bone allografts in their surgical techniques for anterior spinal fusion.

In the 1950s, Drs. Cloward and Crott [ph] popularized the bone dowel shaped allografts that were routinely derived from the ilium, humerus, femur, or fibula. Others, such as Smith and Robinson, recommended ring or wedge-shaped grafts derived from the femur, tibia, or fibula. Such has been the mainstay of spinal surgery for half a century.

Prior to the availability of precision, pre-cut allografts, the majority of structural allografts in use required intraoperative cutting and shaping using standard surgical tools, such as oscillating saws, chisels, and mallets. The precision of such techniques has always been far from exact. In fact, in many cases, even rough approximations of optimal shape were accepted

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to expedite surgery.

The intraoperative preparation of allograft implants is of course done during the operating period under anesthesia and during wound exposure. We have been mentioning that several times today.

In addition, since the required shape to be cut is determined very often after the patient's own bone has been decorticated, the allograft preparation is done during a time of relatively heavier blood loss.

This preparation process therefore involves a well-established risk of greater blood loss, increased likelihood for infection, and increased anesthesia risk. During informed consent for surgery that may involve intraoperative preparation of bone, our patients are fully explained the additional risks of the graft preparation process.

The availability or precision pre-cut allografts has markedly reduced the risks associated with anterior spinal fusion surgery. As I have already mentioned, they have reduced our own operative times and surgical blood loss. The grafts are precisely cut and shaped, such that a more reliable interference fit is achieved than could

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be achieved by self-cutting these grafts in the operating room.

For this reason, these grafts have often obviated the need for adjuvant internal fixation instead of performing both anterior and posterior surgery with pedicle screw as shown in this slide.

Properly fit grafts, such as the threaded bone graft shown in this slide often provide sufficient stabilization, thus in many cases, the fusions performed with pre-cut bone graft materials can be done with bone alone and without adjuvant metallic internal fixation.

This advantage, of course, shortens surgical intervention and shortens recovery times.

My colleagues and I believe that structural allografts are far superior to the widely used metallic interbody fusion devices both biologically and mechanically.

From a mechanical standpoint, the compressive strength of cortical allografts generally exceed physiologic loads. The compressive strength of cortical allografts are comparable to metallic intervertebral devices. The allograft is shown here in the green bar.

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Finally, the fatigue loading values are similar, if not superior, to alternative implants. Pre-cut allografts are shown in the farthest on the right.

Most important in my mind, however, bone graft materials are biologically superior to metallic device products because of their capacity to incorporate to host bone, to remodel according to physiologic loads, and to ultimately resorb.

This, in the prior histologic section from a primate's final model, demonstrate the capacity of allograft implants to completely remodel and resorb following fusion of the intervertebral space leaving only native host bone.

In this example, no remnant of the allograft implant is evident at the fusion site. In contrast, metallic implants, because of their rigidity and permanence, pose a life-long risk of a stress riser bone-metal interface failure. This risk increases with age-related bone mineral loss and is certainly higher in post-menopausal women with progressive osteoporosis.

My genuine concern is that limited access to pre-cut allografts will encourage surgeons to increase

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their use of metallic interbody fusion devices. I strongly feel that this change would not be in the best interests of our patients.

In my practice, if my access to pre-cut allografts becomes restricted, I will continue to implant shaped cortical allografts using the surgical techniques of a decade ago. My colleagues and I will once again inform our patients of the risks associated with intraoperative preparation of allograft bone implants.

We will have to explain to our patients that pre-cut allografts, despite their well-established advantages in our hands, are no longer available because of regulatory concerns. Our most difficult task will be to explain to them the logic of such regulation. Hopefully, this will not be necessary.

Thank you for your time and attention.

DR. NOGUCHI: Thank you very much, Dr. Sandhu, and I thank everyone for continuing to be remarkable in keeping on time.

Our next speaker is Mr. Jens Saakvitne of Life Alaska, and representing both Life Alaska and I believe another physician associated with it.

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Life Alaska

MR. SAAKVITNE: I am Jens Saakvitne. I am Director of Life Alaska, which is a nonprofit tissue and organ donor program covering the State of Alaska. Life Alaska paid for my trip down here.

The Chairman of the Board of Life Alaska is Dr. David McGuire, who is an orthopedic surgeon who specializes in arthroscopic knee repair. He also asked me to share some of his views as an orthopedic surgeon.

Dr. McGuire has been performing ACL reconstruction for about 18 years or so, I believe. In 1990, he started to get fairly heavily into allograft or at least made some very serious moves into it. At that point, he hired a full-time researcher, who remained on staff, and I believe in 1997, he put on a second full-time researcher, so Dr. McGuire makes every effort to go ahead and back up his thoughts and his guesses with facts.

If you follow the transition he made from back in 1990, 4 percent of his patients who needed an ACL reconstruction received an allograft. For '98, '99, and so far in 2000, it is over 90 percent of the patients

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that come in with a torn or destroyed anterior cruciate ligament, are not only given the option, but normally strongly encouraged to receive an allograft or a transplanted tendon.

During this period from 1990 through now, he has done just over 900 ACL allografts using almost all allograft patellar tendons or hemi-patellar tendons. During that time, he has had zero graft failures, he has had zero infections where he feels it was related to the graft.

So, the numbers which are published in Arthroscopy -- unfortunately, I don't know the citation -- are pretty strong.

Why is Dr. McGuire and myself here talking about patellar tendons and knees? Well, contrary to what was said at the very beginning as far as it seemed fairly clear that most tissues or many tissues would not fall under the new guise of device, there is a great deal of nervousness, there is a great lack of understanding or clarity as far as what the final decisions will be.

This why we welcome this opportunity to go ahead and share our views now because if the decision is made

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that, yes, to go ahead with the wording, then, the door is closed, we no longer have a say. We may be surprised by the ruling, saying that if you take an extra-articular ligament, such as the patellar tendon, you put it into an interarticular joint, does that make it non-homologous.

We don't think so, but we don't know. What if you take a tendon and use it as a ligament, does that become non-homologous, if not now, maybe interpretation two years from now or five years from now, don't know. It definitely concerns us.

Why, as a tissue bank, would I care at all about speaking here? Financially, to the best of my knowledge, where we don't have any processing, we do a small amount of courtesy distribution -- I think that is 1,200 pieces of tissue a year or something -- there would not be any real financial incentive.

My biggest reason for wanting to come is that in the last 21 years, I talked with something over 2,000 decedent families, most of whom have become donor families, stayed in touch with many, many of those families for multiple years, remain absolutely amazed and overwhelmed by the compassion and courage these families

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show, and I feel that a trust is put in me, a trust is put in most tissue banks and most coordinators and most people that go ahead the offer the option of donation.

When families accept that option in this terrible, terrible time, they are saying do the right thing. To me, in talking with them, both at the time and afterwards, they are saying help people with it, and I think we need to take that charge and say okay, how can we help the most people in the safest way.

Does this mean reducing safety standards? No, nobody wants that, but does it mean working as a close team with the FDA, with AATB, with everybody, to say we are maximizing the benefits that come out of this? A strong yes.

As you can see, I am not going to beat a dead horse again as far as having a surgeon or having surgical assistant perform the graft, we know about the advantages. It has been presented many times as far as the advantages of having tissue prepared outside and prior to the OR.

The only thing that maybe has not been mentioned is that while surgeons are way too good to ever

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accidently drop a graft, I have heard rumor that that happens to technicians. If it is done in a bone bank, they can go ahead and discard that allograft, prepare another one. You don't have a patient on the table where you don't have other options.

Again, just finishing up the argument of why it makes sense to have allografts prepared elsewhere, the obvious concern if this pushes it over into a device, we will go back to getting raw allograft or even autograft in the operating room.

One of the things that Dr. McGuire wanted to stress is that with the tissue that is being used currently, there is no additions of drugs, chemicals, the changes, the function of the tissue.

Many, if not most, of the shapes are based on what they started off doing with autograft tissue, and then they have carried it over to allograft and are making some minor revisions on that.

You get into some of the more interesting forefronts. Composite grafts can have many definitions. In this case, what we are talking about is a combination of either autograft and allograft tissue or two pieces of

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allograft tissue.

Currently, Dr. McGuire has done several cases where he has taken an Achilles tendon, used that for one bone plug in the tendon, and then up in the tibial tunnel, when he drills that out, he will go ahead and save the core, knots that, and pass the Achilles over that, so you are running into the mixture composite.

You could do the same type of composite using two different pieces of allograft. How is that going to be viewed in the future? Are the regulations going to allow innovation and the continued development of technology for the patient?

One of the things that the Achilles tendon composite has done is relieved a little bit the incredible demand and shortage of patellar tendons for ACL repair. If this technique continues to develop and catch on, we may be able to use some of the other tendons that don't get used as much, anterior/posterior tibialis, et cetera, that with innovation, it will allow us to go ahead and figure out more ways to solve problems, reduce some of the shortages that we are having currently for tissue.

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It also gives the donor family the gift of having more of their gift honored, more of their gift used.

Lastly, a number of different places are looking to or are currently taking bone, adding screws to it. Hopefully, we will never have to get back to the mid-eighties, like Dr. Vich, and start adding the screws right in the OR. We have a capability and expertise to do it in the Class 10 clean rooms. I hope the regulation will be a partner with us and allowing that.

In closing, I would like to touch on two points. One, especially when I attend meetings concerning organ donation, they talk about life saving versus life enhancing, and tissue kind of gets brushed to the side a little bit as life enhancing.

Having worked a great in a medical examiner's office, in Alaska, there are approximately 2,500 deaths a year with a population of 600,000. There are in any year at least 25 deaths from people that have either back injuries, hip injuries, knee injuries, and are just unable to manage pain control.

Whether or not a suicide, whether or not it's

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prescription drug overdose, whether or not it is alcohol overdose, don't know, but it is a huge and probably underreported problem. Some of the surgical techniques we are talking about that are state of the art, they are addressing some of these issues, the cause, chronic disability, chronic pain, take away a person's life, take away a person's dignity.

We can't underestimate the cost of moving backwards on some of this technology. Again, I think we have to do that as a partner.

Lastly, if I were to take a piece of tissue, a product, something, what is it? To a doctor, it may be a crock dowel if he is about to use it. To me, to a certain family, that's a 42-year-old woman with auburn hair, who was walking with her husband by a salmon stream, holding hands, kids behind them. A pick-up truck went out of control, traveled 50 yards off the highway, struck her and her husband. Her husband was thrown to the side. Wife was killed.

I talked to the husband by telephone seven hours after the event. He told me the rest. He told me how he remembers flying through the air, when landed, his knee

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felt funny, it hurt, but he knew that his wife had been hit. He had seen her being thrown, and he looked for her, and all he could see was a pick-up truck that was now straddling the stream, and he was yelling for people to help, and there were a number of other fishermen around.

He said the fishermen gathered around this truck looking for his wife, and then over the course of the next few seconds, his wife's body came drifting out from under the pick-up in the current of the stream.

These fishermen pulled his wife to the side of the stream and knelt down next to her, and this is about, I don't know, 15, 20 feet away from the husband, and attempted to do mouth to mouth breathing for this women.

Unfortunately, she had an eggshell fracture of the skull, the fractures were so bad they simply could not form a seal, and the wife was declared dead at the scene.

They had just moved up there. She had gotten a teaching job, everything was going so well, and then this happens. This man's, this family's life had fallen apart. I talked with him within a few brief hours and in

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spite of all that incredible loss and pain that I can't even begin to imagine, two of his comments to me were please go out and help somebody with this. Then, he said this is something that would have been special to my wife, I like thinking that she is making more of a difference.

I think we can continue in a partnership with the FDA, with technology, with surgeons, with transplant programs, with donor programs, and if we have the open communication, I really think we can help to honor these families and give some really pretty neat gifts to the recipients.

Thank you.

DR. NOGUCHI: Thank you very much, Mr. Saakvitne.

Spinal Patient Recipients of Allograft Tissues

Our next three presentations are going to be from patients and recipients and donors.

The first one, unfortunately, the recipients are not able to be here. These patients were unable to attend the meeting, so they had a home video made. It is going to be showing Melinda Taylor, who is an allograft

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recipient, Lisa Wasshausen, who underwent an autograft operation, and Marisa Taylor, an other allograft recipient with her doctor, Dr. Raymond Woo.

[Videotape played.]

DR. NOGUCHI: Thank you very much, if we could have the lights, please.

Our next two speakers, I would like to thank them both for taking the time and effort to come here today. Sometimes it always seems like the FDA may be an unapproachable object somewhere inside the beltway, but we are very pleased to have both of you.

A Donor Dad and His Story

Our next speaker is Sheriff Stephen Oelrich, and I understand you are a donor father, is that correct?

MR. OELRICH : Right.

My name is Steve Oelrich and I am the sheriff of Alachua County, which is in Gainesville, Florida, and I am also the Chairman of the Gift of Life Committee for the National Sheriffs Association.

RTI bought my ticket to come here to speak, depending on your perspective, either they are in my county or I am in their county, and so I am speaking

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really on behalf of the National Sheriffs Association about this issue.

Before I do that, I want to tell you about my perspective on this and how I got to where I am today based on being a donor dad. That is what I am here about today, is not being the sheriff or chairman of that committee, but as a donor dad and what it means to us as the donor community, donor family community, about this issue and the larger issue of government regulation and sometimes over-regulation when we are faced with this shortage of organs and tissues to go around.

You see, my story started on Father's Day of 1995. I got that call that every parent dreads, and it starts out with, "There has been an accident." Now, I have been a cop for over 20 years, 23 and some years, and I have made that phone call, but I know what it means when they make that phone call, and I knew right off the severity of the situation.

You see, my son, Nicholas, who was 18 years old, went off on a high school, post-high school trip with a bunch of his friends to Cancun, Mexico. There, he and a young lady fell off a balcony after a night of partying,

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and the young lady fell and landed on her feet and smashed her hip and smashed her knee, and she has gotten a hip replacement and will face, as you all know -- she was 18, many more before her life is over.

So, I went to Cancun, Mexico, to get my son back, and I went to retrieve him there, and they told me there that he was what they call brain dead. I brought him back with the help of Shands Hospital in Gainesville, back home where he was born. He was born there and I wanted him to die there if he had to, just down the street from the hospital where he was born.

The doctors there never gave me any hope. He was declared brain dead and I was approached, as a parent, about donating his organ and his tissue, and I said yes. We had not discussed that, but that's the type of kid he was. He was a big, strong kid. He had lettered three years in high school football, and he was also a weight lifter. He was 6 foot 2 and weighed about 220 pounds.

After I made that decision, they immediately or after they got the proper certifications, and so forth, as to his brain death, they took his heart, they took his

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lungs, they took his kidneys, they took his pancreas, they took his stomach, and as we are hearing today, they took his bone.

102 people since that time have received either the gift of life through organs or life-enhancing gift through his donation of his tissue. I have never looked back and regretted that because things that happened after that reinforced that we -- he -- did the right thing.

You see, one of the toughest things for a parent to do is to go through your kid's stuff after they have died, and my older son and I went through his things, and I was amazed, one, about how little an 18-year-old really has, and, number two, I couldn't find a lot of the things he had. Where were his Garfield books? What was his boombox? Where was his pellet rifle? Where was his fishing rod?

Now, the truth of the matter was that he had given those things away or he had loaned them out. You see, during his life, he had given little bits of himself away all during his life, and then the final analysis, he gave us everything he had.

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Now, my role as the chairman, it's a long story. I got to be chairman of the National Sheriffs Association Gift of Life Committee, but our role is, is to spread the word throughout the United States as far as Oregon, tissue and blood donation and the importance thereof to sheriffs' offices with the cooperation of the medical community throughout the United States.

During the month of December we put these on marked cars, sheriffs' cars. We pass out donor cards. To this date, we have passed out 75,000 donor cards, and we put bumper stickers on over 3,000 marked sheriffs' vehicles throughout the United States, but we have got a lot more work to do.

What I am here about today is kind of a trend that I see, perhaps with the government, and it started out with my concern about the HHS and their regulation of organ donation. I heard some things today from FDA staff here that concern me.

One of them is -- and I tried to get this down as best I could -- one staffer quoted, "The difference between human bone and metallic or ceramic is no more than the difference in material."

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For me as a donor dad I find that offensive. Another quote. "If you change a tissue, it is no longer considered a human tissue." It is painful.

We talked about products today. We talked about devices. We talked about tissue products. As far as a donor family, that is a killer.

My role and the role of people like me is to get more donors, get more people signed up, and the more we regulate, restrict, confine, make it harder to make these donations, the tougher it is going to be.

My son was able to give 102 people this gift. I can't tell you how disappointed I would have been that I found out that government regulations only allowed 40 people or 60 people to get them, not 102.

The good news, as you know, as far as organ donation is, is that we are up to about 20,000 procedures a year. The bad news is, is that there is about 70,000 people waiting.

You know, we do a thing at the Alachua County Sheriff's Office where we take a K9 into the pediatric wards and visit the kids that are in those pediatric wards, and some of them, a lot of them are waiting for

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transplants.

Now, I know they don't necessarily want to see the sheriff, but they sure do like to see that dog, and we take a picture of them with the dog, a polaroid, and give it to them, and you can see some of them have a collection of two or three since we go in there once a month. Unfortunately, some of those kids never leave that hospital.

As far as tissue goes, we have heard here today that 100,000 or more procedures are done, hundreds of thousands of procedures are done every year, and I don't want even more people than that waiting for these procedures.

See, what we don't need to do is take the human element out of this by talking about products and devices. We need to put the human element in it, because that is what we are all here about.

I sometimes see government involvement in this things, I know there is a need for regulation, but I don't want a manufactured crisis that begs for government regulation when none is required.

I think this is a medical question, and not a

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government question. It's a human question. I want to do everything I can to increase the numbers of organ donations, tissue donations, and blood availability throughout the United States, and the sheriffs in your community want the same thing.

That is what I am here to push. I hope you will agree with me.

Thank you for your time.

DR. NOGUCHI: Thank you very much, Sheriff Oelrich.

Our last speaker is Mrs. Chrstine Blackgoat, another donor parent.

Donor Parent Testimonial

MRS. BLACKGOAT: Hello. It has been a long day, so I am going to try to be brief.

My name is Christine Blackgoat and I am a nurse and a donor parent. I have come 4,200 miles to talk to you today for 10 minutes at approximately the cost of $310 a minute. Fifty percent of that expense is on my own, and the other half is split by Life Alaska, a not-for-profit organ procurement organization and a donor.

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We would not be at this juncture today but for the difficult decisions and sometimes courageous decisions families make at very tragic times, also, were it not for the foresight of the donors themselves when they let their families know what their wishes would be under those circumstances.

I would like to share with you the circumstances, questions, and influencing factors that donating families frequently face. In the case of donor parents, the circumstances are often sudden, unforeseen, and untimely.

Remember your surprise when you heard about JFK, Jr.'s accident or Princess Di? Well, now imagine it's happened to a loved one, someone near and dear, someone too healthy, too young, too full of joy to die, and you will glimpse the incomprehension that most donor families face at that time.

As a nurse in pediatric intensive care unit, I learned early on that the questions parents asked when I was soliciting for a donation often seemed to range from the mundane to the extraordinary, and yet, when I found myself in that position, I had the very same questions,

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questions like will this delay the funeral, how much will this cost, who will get the tissue and bone and organs, and the impossible, will this hurt my child.

Finally, the two major influencing factors at the time of the decision is what would my loved one have wanted and how do I make sense out of a seemingly random meaningless event. Accidents that take us unexpected happen because of mechanical failure, a moment's distraction, an error of judgment, but their finality lasts a lifetime.

My son, Ben, was a 6 foot 3, 17-year-old radiant human being. As a regional cross-country champion, he had Olympic aspirations and ran 10 to 15 miles every day. The day before Thanksgiving in 1996, on an after-school routine training run, he fell 350 feet to his death off the Perseverance Trail in Juneau at 2:30 in the afternoon.

The last words he said to me that morning is, "Mon, is it okay if I take time for a run before I go to choir practice?" Going through, as Sheriff Oelrich shared with us, opening his desk revealed many things about my son that I had either not known or forgotten.

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In his desk was an application to Notre Dame that was partially filled out, and also he had signed up for his draft card, but stuck a Post-It note, "Do not sign," because he was one month away from his 18th birthday.

But in one case his foresight as the youngest of five kids and having learned from the mistakes of all the others, really provided me with a lot of peace of mind, and that is, at the time he took his driver's license tests, in Alaska, you can sign up to be a donor right then, and he said to me, "Mom, why would anybody not sign this? It's the only thing that makes sense."

Well, being a gregarious kid, he managed to convey that to every one of his siblings, as well, because he was so fascinated with the idea that maybe some people wouldn't sign up.

This made a decision that could have been difficult a lot easier when his father had very different feelings about the donation, because it made it possible to us to honor clearly what he would have wanted.

Now, the FDA is faced with some difficult issues, but I hope the regulations we come up with make

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sense, because rather than tissue or devices, the allograft bone is my son's legacy, the only one that he was allowed to make in his brief life.

it is my understanding that the FDA's primary goal is to provide additional protection for the public without unduly or unnecessarily imposing restrictions on the development or distribution of bone.

This implies that there is a public health issue. As a nurse and a donor parent, the public health issue that I see are availability of the allograft bone, the timeliness with which it is given to recipients to help alleviate their condition before it deteriorates, and so if that is the public health issue, then, I think what needs to be done, I can no reason as a nurse or a donor parent for further regulation until such time as cause is shown that use of allograft bone needs to be restricted.

Regulation often brings with it quarantine, and it would be very difficult to get additional donations if it becomes the image of stockpiling or bones, organs, and tissue in banks and putting them under quarantine would be a great deterrent to many families from contributing.

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Three weeks after my son died, I received a letter from Life Alaska, and in that letter I learned that his donation of bone was going to allow a grandfather to dance at his granddaughter's wedding.

Thank you.

DR. NOGUCHI: Thank you very much, Mrs. Blackgoat.

I would now like to ask the final FDA Panel to step up to the plate here and we will be almost finished. I think all the panel speakers are not quite finished yet.

Questions from FDA Panel

We have dutifully made everybody else tell us who they are. I think you have seen many of the panel speakers or FDA panel members before. I give you Dr. Zoon's apologies for having to leave for another meeting, actually on bioterrorism. We often have to do triple or quadruple duty.

David Feigal. You have already seen myself. Mr. Steve Unger, who is the ombudsman for FDA and is in charge of product jurisdiction. Dr. Witten, I believe is up there. Ruth Solomon. Sergio Gadaleta and Martin

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Yahiro, I believe are both from our sister agency at Devices. Welcome.

I am going to start off the questioning with a question for our two donor representatives. We appreciate very much bringing back the personal aspect to this.

In addition to your concern about keeping this a human process, what if you didn't know the tissue processing people in your area, how could you think the government could help to make sure that everyone is as dedicated as those you have heard here today? And is it necessary perhaps is the way to say it.

MR. OELRICH: Well, my situation was I was very blessed and I knew, you know, being right there at Gainesville, the University of Florida, Shands Hospital, I think this boils down into trust. It does with any patient-physician relationship, medical relationship.

You just have to trust that those people are going to do the things in the best manner and the most ethical manner you can possibly do. There is no way that you, yourself, as a lay person, can check up on the standards and procedures that they are going to do.

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So, I think if the FDA has a role here, or for that matter, HHS, it would certainly be set up the playing field for physicians, parents, and, in this case, donor families, to exercise this procedure, which is literally giving the gift of life or certainly an enhancement of life procedure, and, for lack of a better term, stay out of the way as much as possible or as best possible without regulations.

Regulations, I see myself as trying to get more people to sign up to be organ and tissue donors. We need to constantly see if we can make it easier and more facilitative as oppose to the other way around.

DR. NOGUCHI: Mrs. Blackgoat.

MRS. BLACKGOAT: I think I am going to echo some of the sheriff's comments. I professionally had interfaced with organ procurement organizations for years, and the most outstanding characteristic was that it is a field that tends to attract lots and lots of people that are also donor families.

So, they have both a professional interest and also a person avocation. The extraordinary lengths that I have seen folks go to, in Alaska, we have some very

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extraordinary conditions. We have areas that can only be reached by dog sled or airplane, other areas by boat or airplane. So, what we have to do to transport bodies, to harvest organs, to have an active organization is extraordinary.

On the other hands, we live in a habitat that is relatively unforgiving, and we have some consequences that happen that wouldn't happen anywhere else - avalanches and bears and extraordinary things, so that our young folks from 17 to 23, we have the highest death rate in the nation, and it is due to accident, because of the lifestyle and the environment we live in.

I think that monitoring is not an issue, because I am absolutely confident that every facility in Alaska would stand up to even the most closest, minute scrutiny, and that the ethics involved and the cutting edge knowledge of learning new techniques in the process have always been demonstrated long before I had to interface with these folks on a personal level.

A lot of what they do goes far beyond just providing the allograft bone and providing the emotional support, taking that grief and channeling it into

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productive pursuits. They perform a service, but this would be for nothing if bone were not able to heal and be incorporated into the body.

When we talk about the gift of life, to have something that can be regenerative, you don't get that from porcelain, plastic, or stainless steel. It is also a gift, and I know you are supposed to keep church and state separated, but also a gift of life from whatever higher power or God that you believe in.

So, it is so much more. So, I guess I have gone beyond the scope of your question, but I do think it is an issue of trust and the hours and the unstinting caring that takes place.

DR. NOGUCHI: Thank you, both. I know it is always hard to respond in public.

I would like my FDA colleagues to now take the opportunity, and if you don't have a question, I am going to go down the row here.

Celia, why don't you start.

DR. WITTEN: This is a question for the industry people who are here, which is there was a lot of discussion during the early part of this session, the

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first two questions that we had asked in arranging for this meeting, but not much in the way of comment on the last three, that is to say, risk standards and controls.

So, I am just throwing it open to ask if any of you have any comments you would like to share on the latter three questions that were on the agenda for today.

MR. SAAKVITNE: I can speak for Dr. McGuire because we have discussed this fairly extensively.

As a surgeon, he has a responsibility if there is a problem with a tissue -- and there have been some problems as far as size differences before -- it is his responsibility to get on the phone with me. I become the go-for as far as contacting the tissue bank that it came from.

We go ahead and write just a little note or report saying tissue report is 45 centimeters, physician measured it at 40 centimeters or millimeters. The tissue bank has to respond to us in writing. To be honest, tissue banks have been fantastic about it, but the surgeon, if there is a problem, he has to start the ball rolling. It is not a matter of buck passing.

DR. NOGUCHI: Other questions from FDA?

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DR. FEIGAL: A question primarily for industry and for the practitioners, which is, is this a product area -- speaking just of the bone, and not of all the different tissues that might be involved in tissue bank -- is this a product area that is so straightforward that all of the tissue banks that are supplying this product, are supplying something that is of equivalent and interchangeable quality, there really aren't any concerns about any of the companies out there, that are providing these services in terms of their quality?

I guess I was asking, as a surgeon I was asking the question, is there anybody whose products you wouldn't be crazy about purchasing, and do you have favorites, which gets at the issue of whether or not there is a uniform enough high level of quality with this type of tissue?

DR. SANDHU: I don't appreciate in my own practice actual differences in quality of burnt bone per se, but keep in mind these are pre-cut and shaped bone materials, and different manufacturers may select a variety of shapes and size that they are going to provide to the practitioner, and based upon that practitioner's

choice or style or approach to the spine, they may prefer one collection or set of choices versus another.

So, I think that is the bigger factor in choosing the source of the bone materials.

DR. FRANKEL: I would want to make sure that the bone bank belongs to the AATB and follows their standards, that they carefully look at the donors, you don't have a donor that has got five tatoos and needle tracks, and that the donor be carefully examined as far as disease or infection, and perhaps some banks are more vigilant than other banks, but I think if they all follow the AATB standards, then, I think your safety is ensured and you have pretty much interchangeability of grafts.

DR. NOGUCHI: Any other comments from the speakers to this particular question? Mark.

DR. CITRON: Actually, I was wondering if you had some thoughts about how you define quality, and how would you differentiate quality.

DR. NOGUCHI: Well, I think actually that is a question, most of us are not practicing orthopedic surgeons and really wouldn't have the right perspective on what to consider when are treating a patient. That is

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where we certainly hope some of the practitioners would be vocal about whether there is a concern there or not.

If there is not a concern, that helps us. If there is kind of a, well, I don't think there is a concern, but maybe it would be good to have some standards, we did hear that earlier. So, I don't think we know the answer certainly.

Ruth.

DR. SOLOMON: I didn't have any particular questions, but I just wanted to clarify some of the statements and implications that have been made today.

First of all, FDA is not considering regulating all bone allografts as devices. That is the implication that some of you have put out there today. There are only certain ones that met the criteria that we have proposed would be kicked up to that level. So, that is the first misunderstanding perhaps.

Then, another supposition that is being made is that if bone were regulated as a device, that it would ipso facto decrease the supply, and I don't think that that is necessarily a cause and effect proven given.

The other implication being that we would then

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have to use autologous material or metallic material, so the implication that regulation as a device would decrease the supply of allograft simply is not proven.

Then, there were some statements made by Jennifer Davis on the TRG that I would like to clarify. The first was that Jennifer said that our recommendations are made on proposals, and not what is currently in effect.

I am the co-chair of that group, and I can tell you that that is not correct. When we arrive at our decisions, the decision is based on how the product would fit under the definition currently in effect under the final rule, as well as how it might be viewed under the proposed approach. We would never just make a recommendation based on things that we have not yet finalized.

Also, Jennifer and many other people have mentioned that the TRG process should be more transparent. This quite difficult because let us say, for instance, that the company that Ms. Davis represented were to send information to the TRG that was marked Confidential. We could not in all good conscience reveal

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that publicly. That is just not permitted.

So, there is a fine tightrope that we have to walk between making what we do transparent versus breaching the confidentiality of the bank or the manufacturer that has asked us for an opinion.

Also, Jennifer mentioned that she would suggest that we re-propose the definitions of homologous use and minimal manipulation, giving examples.

Well, we did give examples in both the 1997 document and in each of the two proposed rules that have published.

Also, a statement was made that increased regulation would drive the industry toward intrastate interactions, and I think you should be aware that the final rule and anything we are proposing applies to both intrastate and interstate, and, in fact, my device colleagues could comment, but I believe the device regulations also do not rely on this interstate/intrastate differentiation.

Also, the individual from Telos, who talked about the six-month quarantine from living bone donors, that is not a requirement that we have proposed. The

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only six-month quarantine requirement being proposed is for the quarantine and retesting of sperm donors. For other living donors, we have recommended it, but it would not be required.

Also, some of the procedures that were discussed by one of the speakers, that were done in the operating room, again, FDA is not planning to regulate what goes on in the operating room during the same surgical procedure.

So, those were just some clarifications that I had, and also to point out that of the four kick-up factors that we are now proposing, we would have to go back and think about eliminating two out of the four as some people have suggested today, because all that would leave would be a product, a tissue or cell that is combined with the drug or device, it would leave that one, and it would leave the kick-up factor of systemic or metabolic effect.

So, I think we would have to go back and look at how it would affect our view of the regulation of certain products if we now eliminated two out of the four kick-up factors, would we be missing something that we really did want regulate as a device or biologic. That would then

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become only solely regulated under 361.

I seem to be talking a lot, I hope you don't mind. But when we undertook to develop the proposed approach, we wanted to create an umbrella of decisionmaking processes that we could apply to a whole realm of tissues, as I mentioned before, tissues, cellular products, tissue products currently regulated under 1270, combination products.

Now, maybe it might have been naive to think that we could come up with something that could so sweepingly apply to this large spectrum of products, but we certainly gave it our best shot.

Now, we are hearing that perhaps the criteria should be spelled out specific to a particular group of tissues, and that is not really what the initial intention was. It was to try to put everything under an umbrella to create consistency.

So, I just thought I would mention where we started from and where people seem to be pushing us to wind up at, they seem to be quite at odds with each other.

DR. NOGUCHI: Ruth, thank you for those

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explanations although just to take a slight different perspective, some of us were here in 19 -- I forget, 1980-something or early eighties when we were talking about tissues and devices, and the whole same sort of thing.

Then, we didn't have regulations. Now, we do for infectious diseases, and to some of us, that is a major step forward. Now we are arguing about the details for how we are going to do it.

So, part of the overall intent was to get past the first hump of really saying, yes, we are going to regulate tissues, and now we are just sort of saying tissues and everything above that. I think there is bound to be some controversy, but what I have heard here today has been very constructive criticism, if you want to call it that.

Sergio.

DR. GADALETA: I guess I have a question for the manufacturers. It was alluded to earlier, but I am not sure it was answered specifically.

It has to do with the intrinsic variability of bone as a raw material. How is the industry ensuring

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that product X from donor X will actually perform as expected in vivo?

DR. FRANKEL: My research area has always been biomechanics, so I have been very interested in mechanical properties of bone. If you look at, take cortical bone, take young bone, and take old bone, and old bone is always 10 years older than I am, if you look at the stress/strain curve for bone, the modulus elasticity is the same for young bone and old bone.

One you pass the yield point, you can pull out the young bone about twice as much as you can pull out the old bone, but the main thing is you want that elastic portion showing the bone is just as stiff.

Now, if you take a femoral ring and you want a 1-centimeter femoral ring, you have to have 1 centimeter of bone there. The other thing you do is you kind of restrict the age of the donor. Apparently, I am no longer eligible. That comes into play.

Now, cancellous bone, again, you are not going to take a femoral head of an 85-year-old woman and expect that to be a good graft. So, there are mechanical properties of these things that you don't really have to

test in there, but you know from previous studies - age related, osteoporosis, and sizing.

DR. GADALETA: Doesn't the screening account for that, where they won't allow an individual who is over X years of age or is osteoporotic, et cetera?

DR. FRANKEL: Yes, I think at MTF, we have a restriction on the upper limit and also we don't want people who have had tumors or metastases, even though you are going to process it, and you don't have a metastases of the bone that you know, you still don't want to use that bone if people have had infections. So, I think there is very good controls, yes.

DR. NOGUCHI: Last question? Martin.

DR. YAHIRO: I feel like we are all indebted to the donors and the donor associations that are able to supply us, as surgeons, and as patients, the donor material that we are talking about.

I think there is a lot of good information that the FDA can take away from this meeting, that I don't have any further questions.

Closing Remarks

DR. NOGUCHI: If the panel will indulge me, just

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a few more closing remarks.

I would like to thank everyone here for lasting through the day and contributing vigorously to this discussion. FDA does not regulate the practice of medicine, but we do regulate those products that come into your hands and that you use to treat your patients.

As we have seen, we have taken a somewhat cautious approach with tissues because it is very closely aligned to the procurement of human organs, which FDA really does not regulate.

So, as we go forward, I think it is no surprise that things are going to have to be worked out, we hope not necessarily on a case-by-case basis, but on a way that we can continue to move forward in a very productive manner without compromising the supply of tissues to needed individuals.

As I mentioned before, we now all accept the fact that infectious disease control, it has gone from the, well, we do this ourselves, to, of course, everybody does that, that is why we have the final rule. To many of us, that is a tremendous step forward.

Now we are starting to get into the questions

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where traditionally, FDA, we kind of think, well, those are what we ask of our product, I would like to know about the biological potency of this preparation versus another, or if, in fact, I am using something that is machined to a specification, I am not quite sure if I like this machining better or that one, how do we compare between different companies, different procurers, and so forth.

Again, traditionally, FDA has seen those as product related issues, but we are learning on how to do this in a less -- what some would call obtrusive, but really, a more streamlined fashion.

So, we are in the learning process, too, as well. I think there has been some consensus that we have heard here today. I didn't bother counting up, but I think we asked the question about two definitions we had proposed as kick-up factors, and we had some concerns raised from the level that we have concerns about this, maybe we need more discussion, to fears that this might compromise the tissue supply, all of which, as Ruth has indicated, we are going to listen to very -- well, we have listened to it very solemnly, and we are going to

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try to work and deal with those issues.

I think it has identified a point that needed to be discussed and is now being discussed quite vigorously.

We appreciate very much the support for the GTPs and all I can say on that issue is we are as anxious to move that and get it out in proposed form as every one else. We do recognize, as well, that that can help to set many of the standards and really set the playing field, so that we won't have to worry about if you do it in Alaska, we already know it is going to be done right versus somewhere else.

Finally, I guess that there was a call for more transparency particularly with the Tissue Reference Group and others. The agency in general wants to be as transparent as possible because what we have found is that if people understand what we do and why we do it, there is usually absolutely much less controversy and people may still not agree, but at least they know what they are not agreeing to.

I think Ruth identified one of the conditions that if you want more transparency at the TRG, just remember much of the questions come about when you have

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innovative, new technologies or combinations or different ways of processing.

Most of the time in the past, companies and sponsors have considered that to be commercial confidential and/or proprietary and/or both. If we are going to open up, it is very, very difficult to say why we make decisions unless we can also talk about the specifics of what is being proposed.

So, I think FDA would say we are willing to do that sort of thing, but our current regulations would suggest that that is a major stumbling block, but if that is, in fact, what Ms. Davis from Hogan and Hartson would like, we will work with her on that particular issue.

Finally, as it is getting late in the day, I would like to on behalf of Dr. Zoon and Dr. Feigal and Commissioner Jane Haney, we appreciate this, we have heard you, we will be working with you, and we will get back to you.

Thank you all very much.

[Whereupon, at 4:43 p.m., the public meeting was adjourned.]