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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

PROPOSED APPROACH TO REGULATION OF CELLULAR AND TISSUE-BASED PRODUCTS

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C O N T E N T S

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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

Opening Remarks

MS. PENDERGAST: Good morning, everybody. We are starting a little late but it is still earlier than I could ever think possible that I would be standing up talking to somebody. So this is "meet the regulators while they are still too sleepy to talk back."

So, good morning. This is our public meeting on tissues and cells. We are here to learn from you, to receive your comments, criticisms, suggestions on the approach that the FDA is planning or thinking about taking with respect to regulation of all cells and tissues.

How we got here? What I supposed to address is somewhat of a complicated and tortuous path. You know that this is an industry that has its roots in some types of medicine that are very old, but it is also a type of therapy that is exploding at the boundaries of biotechnology.

We regulated some parts of it but not others. We regulated in two centers with two different laws with sometimes two different sets of standards. Several years ago, we put into place interim rules which took care of some of the worst of the infectious-disease abuses but it

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didn't cover all tissues and cells. So we still have infectious-disease issues hanging out there.

Then Congress began to look at the issue and we were looking at it with them, briefing them, talking to them. And we realized, in the course of those discussions, that we weren't fully satisfied with our approach, that it could use some freshening, some change.

So, after Congress left town last fall, we began to intensively look and said, "Okay, what could we do here? How could we regulate all tissues and cells in a way that would make sense for the agency with our limited resources and that would make sense for industry that could be put in place for the next five years?"

We can't expect anything to last longer than five years anymore, but what could we do that would last for five years that would give guidance to the industry, that could keep the FDA focused only on the high-ticket issues, the most important risk issues, the most important benefit issues and triage, basically, our involvement.

We came up with a scheme, an approach, a conceptual approach, which we put in the Federal Register a couple of weeks ago. Some of you had an opportunity to talk to us about it at a couple of meetings that the FDA

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held in December and then, again, in January and early February. Others of you have not.

We are especially interested in hearing today from those of you that we have never spoke to but certainly we welcome the criticisms and suggestions from all of you.

With that, I am going to stop, introduce Amanda who will give a few things. We will have another couple of discussions and then I will do what I call my Vanna White as I explain the program or the cellular construct.

Amanda?

MS. NORTON: Thank you, Mary. As some of you may know, I am the chief mediator and ombudsman for FDA. Part of my responsibilities are to make jurisdictional decisions about products and to work with the centers to sort out any kind of jurisdictional issues, whether they are combination products or simply products that there is a question about and so that is my role here this morning.

I want to just sort of focus a little bit on what the jurisdictional issues may be and to give you a little bit of a framework so that, hopefully, we will then be able to hear from you suggestions on how to shape our process to be most responsive to your needs.

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We set up a process about five years ago that has both the intercenter agreements and a regulatory part in 21CFR Part 3. That is a 60-day process which was one of the critical elements that was important to use in adopting it. It is a self-executing, 60-day process, so it keeps it short.

And the other hallmark of that process is it is voluntary. Companies can come in to us but there is no requirement that you do so. There is obviously hazard if there is a jurisdictional question that is unresolved. There is hazard going forward and it certainly is our belief that as early and as quickly as we can resolve any jurisdictional issues, it benefits all of us.

So, considering this area with cells and tissues, we thought it was important to embody that spirit that led us to set up the earlier one but to create a special group called the Tissue Reference Group that is kind of a subset of this process to help work through any of the issues that are likely to arise.

Given the triage outline that Mary talked about, I think it is likely there will be issues as to how you resolve what category, what box and so forth.

So, first, let me introduce the Tissue Reference Group so that you will have a sense of who they are. Phil Noguchi from CBER has very kindly agreed to chair

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the group on an interim basis. Joy Cavagnaro is also on it from CBER but I don't think she is here with us yet this morning. And Antonio Pereira, also from CBER.

From CDRH, we have Claudia Gaffey and Celia Witten, and Gene Berk here. From my office, seated in the first row, we have Steve Unger and Andrea Chamblee who will be working very closely with them bringing their long-standing product jurisdiction expertise. And John Bishop from CBER is going to be the interim exec sec with the group.

Now, the thinking behind comprising this group was to be able to address the breadth and extent of potential variation in this area and to do what we could to kind of bring informed decision-making and consistency to the process.

The group combines both the scientific expertise and regulatory expertise as well as the jurisdictional expertise which, over the last few years, we would have learned a lot in dealing with. We met last week, the Tissue Reference Group did, to consider how to operate most efficiently and expeditiously, how to be most responsive to your questions and how to insure that decisions that get made, advice that is given, is not only prompt but thorough, consistent and reliable.

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In this area, as I think the concept paper lays out, we acknowledge we don't know the full size and scope of the cell and tissue industry and its potential products and that these jurisdictional issues may turn out to be a bit of a challenge. We certainly have learned that over time in other areas.

On the other hand, you all, the manufacturers, developers, will want to know as early as you can, how the agency is going to view your product. So we have kind of a spectrum to choose from.

In the Part 3 regs, which is the regular jurisdictional process, we suggest that manufacturers come in as early as they can describe the product to us so that it minimizes the chance for developmental work that proves not to be useful or necessary.

If there is enough information to describe the product, we can go ahead. If we need more information, we will just ask for it. I think the same will be true here. And so what I think we would really like to hear from you this morning is what the spectrum is, what the range is, what would be useful to you because, to the extent that you have multiple people to talk to in the agency and informal advice, you run risks, risk of misunderstanding and inconsistency.

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On the other hand, at the other end of the spectrum, which is our formal process, is 15 written pages in 60 days which is a self-executing 60 days. That is not necessary for everything. Our real goal, and what I hope you will help us with today, is how to strike the right balance, how to comprise a variety of ways that you can get information from the agency that will be useful and efficient but not ultimately, down the road, turn out to be provocative of inconsistent decisions or erroneous viewpoints or misunderstandings.

So that is why we need to work on that internally to carry out the agency's interests and we are confident we can do that. What we would really like to hear from you today is what your concerns are, what your interests are, what you need, what you want from us in this process so that, when you come to the agency to ask a question about what is your product, you get an answer you can rely on and that you can get on with development that is good for us and good for you.

So I very much look forward to hearing all your comments. Let me just say right now that, unfortunately, I need to leave at noon but Steve Unger, my deputy, and Andrea Chamblee from the office will be here all day so we will certainly benefit from any suggestions you make.

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If you want to make suggestions in writing or contact our office, that, I think, would be very useful and helpful as well.

Thank you.

DR. ZOON: Good morning. Happy St. Patrick's Day. I think it is a befitting time to be discussing many of the topics that we are going to discuss today. My name is Kathy Zoon. I am the Director of the Center for Biologics. I also would like to extend my very best to all of you and thank you sincerely for coming today.

This is a very important topic for us and for you and it is our objective to do the best possible job we can in developing the strategies that we go forth with in the regulation of these products.

So this is very much your meeting. We are here to listen to those things that you feel you need to say about our proposals, embellish, improve, whatever recommendations you think are appropriate and to answer questions that may be confusing about what the approach encompasses.

This strategy, as Ms. Pendergast pointed out, was unveiled last month as a REGO initiative under the National Performance Review. It is our feeling that this approach that has been put out is one which offers greater flexibility in the regulation of tissue-related

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products but which are based on strong scientifically sound principles.

I think this is important for us, one, to insure that these products are managed and regulated in an appropriate level of oversight and, two, that the public has assurance that we are looking after their public health.

In addition, we believe that the scheme that Ms. Pendergast will present in more detail in a few moments will allow the enhanced availability of safe tissues for human transplantation and facilitate the innovation of new cellular products for a wide variety of medical uses.

We anticipate this approach to minimize the amount of submissions into the agency and CBER as one component of it and focus, in a sense, on many standard-setting approaches for a number of these products. In saying that, we will continue to have a more vigorous approach with respect to the cellular and gene-therapy areas as appropriate.

This has been an area of endeavor that CDRH and CBER have engaged in for more than two decades so many of the aspects of the regulation of tissues are not new for us. In fact, I was talking to Dr. Noguchi and we have, over the course of the past two decades, written drafts of two or three proposed rules for the regulation of

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sperm banks. We have had points to consider documents on lymphocyte therapies.

We have also had a number of policy statements as they relate to cellular therapies and gene therapies, human tissues for transplantation, as Mary pointed out, and, additionally, a statement on manipulated autologous cells for structural support.

So I think the agency, over the years, has been actively engaged in these processes, but they have been done in an ad hoc manner. I think what we have really tried to do in the most thoughtful way is try to pull together what we thought scientifically made sense in terms of looking at these types of products and the degree of regulation that would actually be needed for them, that there would be as much regulation as needed to be for certain classes of products to assure their ability to have their appropriate use and their safety.

In doing so, there were areas with respect to communicable diseases, processing and needs for safety and efficacy data as appropriate built into this particular program.

CBER will be a key player. We will, as Ms. Norton described, be a key player with the Center for Devices in both the Tissue Reference Group as well as in the review of these products. We look forward to working

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with our sister center on continuing to develop the framework and the appropriate regulatory documents that surround them.

In closing, I just want to say that we look forward to your comments today. We look forward to your suggestions. It is only if we can make sure that we are really meeting the public needs that this process will be successful.

The help and support that we have received from many different groups along the way that we have interacted with, we have appreciated very much and we look forward to those today who may not have had an opportunity or who had continuing thoughts in this area to contribute this morning.

I would just like to take a minute and introduce some folks at the table who have not been introduced already to you. There is Jay Epstein. He is the Director of the Office of Blood. Then we have Antonio Pereira and Marty Wells of the Tissue Program and Ruth Solomon of the Tissue Program.

I will now introduce Dr. Jay Siegel who is the head of the Office of Therapeutics. I now will introduce the next speaker and colleague, Kimber Richter, who is from the CDRH.

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DR. RICHTER: As Dr. Zoon said, my name is Kimber Richter. I am the Deputy Director in the Office of Device Evaluation in the Center for Devices and Radiologic Health. We have been working as an active participant with the Center for Biologics in developing the policy that we will be discussing today.

We will be continuing to work with CBER to assure consistency and appropriate oversight of these products. As already mentioned, CDRH has three representatives that will be working on the Tissue Reference Group.

We look forward to your comments, concerns and any ideas that you care to offer today, and I would like to thank you for participating. This is an important meeting.

FDA Overview of Regulatory Framework

MS. PENDERGAST: Hello. I am Mary Pendergast again. I am just going to cover briefly our proposed scheme. But, before I do that, let me ask a question. How many of you have read both our English-language version and our scientific version of these documents?

[Show of hands.]

How many of you have read neither our English-language version or our scientific version.

[No response.]

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Great. I am going to, then, run very briefly through this scheme because you have all seen it already. Let me just cover some of the high points.

[Slide.]

This is where we used to be. This was our excellent diagram that tried to get us to figure out where tissues and cellular therapies fell. I couldn't follow it. I figured if I couldn't follow it, maybe other people couldn't either. But it was an attempt to develop a product-based conceptual approach, different approaches depending on different product lines.

That is what we are basically getting rid of. What we are doing is we are going to have one scheme that will cover all cellular and tissue-based products with several very notable exceptions. We aren't covering whole vascularized organs. They stay at HRSA as does bone marrow.

We also are not going to cover the skin transfusable blood products which are already heavily regulated by the FDA and we are leaving those aside, at least for now. We are also not going to cover animal organs or xenotransplantation. We put out guidelines last year. And we are not going to cover secreted or extracted products which are things like collagen growth factors and breast milk.

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So, with that aside, we are covering the rest, the spectrum, of cellular and tissue-based therapies. Our proposed scheme is going to be one unitary scheme, so you can quit looking at this. It is going to be one unitary scheme that is a tiered approach based on risk to the patients and to the public health.

One of the things we realized about our old scheme was that it didn't necessarily treat like products alike on similar attributes. We tried to have a scheme where, I think conceptually, it was a little bit like muscles, like bone, like this, like this, and then you would chop off at a certain point and say, "We won't regulate the simple ones. We will regulate the hard ones."

That ran us into troubles because sometimes even simple ones present complex infectious-disease issues and vice versa. So we are trying to treat all tissues alike on similar attributes. We are going to keep standard setting but we are going to abandon submissions.

We have cleaved the connection between standards and submissions except in areas of highest concern. We have set up a scheme that, hopefully, will enable us to lessen regulatory oversight as science progresses and we are going to be able to improve public health.

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For example, we will be regulating for the first time sperm banks for infectious-disease control. As you have already heard, we are going to do our best to have consistency across the agency with our Tissue Reference Group.

Now, in devising this scheme, we had little or no reports to devote to it. The Center for Biologics and the Center for Devices employees already work very, very hard, nights and on weekends. We don't have any new FTEs. We don't have any new appropriations. So anything that we do in this field has to be taken from something else that we do.

So it is critically important for us to be able to triage our resources and to use them only when we absolutely had to. The other thing that was really important to us was to be intellectually honest and to try and make decisional rules that would cover everybody and that we would have as few "yeah, but," "yeah, but," "yeah, but,"s as possible.

Let me talk briefly about your industry. As you know, you have got a wide spectrum of tissues. There are people here that do conventional tissues like bone, tendon, skin grafts and then the high-flying technology and gene therapy.

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There are a wide variety of uses, everything from its original use to highly sophisticated potential cures for cancer, Parkinson and genetic defects. It is a technology that is exploding. We see articles now in Science, Newsweek, the Today Show. Yet, while the science is exploding, there are also high outrage factors. People still worry about the fact that cells and tissues can transmit infectious diseases and there is also the high outrage factor when the government steps on family matters.

As you know, the FDA has been under scrutiny about what we are going to do about this for a number of years. GAO criticized us because we didn't even know who was doing what. And other members of the Hill, at some of your behests, were attempting to introduce legislation in this area.

Last, I would just like to point out that there is an international component to this. Other parts of the world also recognize that they have got to do something but they don't quite know what.

[Slide.]

So, with that, what we did is we abandoned our old scheme and we have created a scheme where we have five areas of product concern. Instead of trying to have

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a unitary system, we said, what are the things that matter most.

These issues, as presented in our English-language version, our REGO document, is does the tissue pose the possibility of transmitting communicable disease, what processing or handling controls need to be in place, are there safety issues other than infectious disease or efficacy issues that would require an independent FDA review, what kinds of promotional claims are being made and then who is doing what, how can we know who you are and how can you learn from us by having us have your name so that we can send you things.

For each of those five areas, we are asking three questions: what are the product characteristics; what, if anything must industry do; and what, if anything, must industry submit to the FDA.

So, with respect to the product characteristics, we realized that there were a few product characteristics that have an impact across the entire spectrum. The first one is autologous versus allogeneic versus family-related allogeneic. In other words, is the tissue coming from your body back into your body, from somebody else's body into your body or is it body parts being shared among family members which we call family-related allogeneic.

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Is the tissue viable or nonviable. Obviously, viable tissue presents more infectious-disease concerns than nonviable tissue. Homologous or non-homologous function or, as we say in our REGO document, is it the natural function or a non-natural function.

Banked or unbanked. That matters because you have the two different sets of concerns when it is banked. One is all the healthcare workers that work at the bank. Secondly, you have the capacity to transmit disease from one tissue to another. You have the possibility of mixups if you don't label it. So, banking, itself, creates extra complexity.

Minimal versus more than minimal manipulation.

Eric Flamm is here. Dr. Flamm was critically important in getting these documents written and helping us think through the issues. So, welcome.

Minimal versus more than minimal manipulation has to do with how much manipulation of the product you are doing. It is one of the areas where we will have a lot of deregulation over time.

Then, whether it is structural and local, metabolic or reproductive and, finally, is it something that is combined with other cells or tissues or combined with a device or combined with a drug because that adds another level of complexity.

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[Slide.]

Let me just briefly, since you have all read this thing, go through the direct transmission of communicable diseases. What we tried to do is, again, we tried to triage. On the top of the page, there is less regulation. At the bottom of the page, there is always more. So we said with respect to communicable-disease transmission, if it is surgery, something going out of your body back into your body right away, industry has to do nothing and you don't have to submit anything to use.

The second group is autologous--that is to say--from the same person where is it banked, processed or shipped. There we recommend but don't require testing because obviously it is leaving your body going back into your body.

But we do recommend it because it is going to be banked, processed or shipped, and you have the capacity to cross contaminate other tissues. You also have the capacity to harm healthcare workers. But there are other ways around that.

So there are some controls to protect other people in the labeling. But, again, you don't have to submit anything to the FDA. This shows the cleavage between what you have to do and what you have to submit.

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We will set standards for infectious-disease control and they are in the documents that you have got.

You are going to have to do it but you don't have to tell us that you do it, although, were we to come and inspect, and I can get to that a little bit later, we would check to make sure you were doing it. Also, if you failed to do it, obviously there are lots of tort lawyers that have extra time on their hands. State licensing boards and others would probably care as well.

Then allogeneic, it's coming from a different person. There are, obviously, infectious-disease concerns there so there we require testing. Again, no regulatory submission. Finally, if it is allogeneic coming from a different person and the tissue is viable, we take into account the fact that it can transmit more diseases, as I indicted, so more testing is required but no submission, again, is required.

[Slide.]

Control of processing. Again, this is, obviously, in a lot more detail in your book, but, briefly, when it is surgery, you don't have to do anything and you don't have to submit anything to us. If you are engaging in only minimal manipulation, you are not changing the biological characteristics of the

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product, then you just have to follow what we are calling good tissue practices.

But, again, you have to follow the good tissue practices which are very similar in large measure, or will be, to what many of the accrediting societies already require. Again, you won't have to submit anything to us. You have to follow it but you don't have to tell us that you do it unless we knock on your door.

Finally, if it is more than minimal manipulation or if it is minimally manipulated but, as you see, there are other things, kick-up factors, such as for a non-homologous use or combined with a drug or device, then the question of constancy and control plays even a larger role. So there we require good manufacturer practices which incorporate good tissue practices but, basically, add on to them so, again, that tiered approach.

There, you are going to have to submit an application to the FDA. We are working towards having a BLA, a biologics license application, not the double product license and established license application, so that BLA/CMC means we are going to the unitary approach we did for biotech products which is to say a biologics license application with a chemistry manufacturer and control section.

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Or standards; now, this is one of those areas where we are throwing it open to industry. We are saying, look, if you guys don't want to all have to submit applications, we can respect that. Help us write product standards for your products, pool your data, cooperate amongst yourselves, help us write standards and if we can write standards based on available information, then we will have a standard and people can basically certify that they meet the standard and they wouldn't have to have individualized applications.

But that really depends almost completely on you and whether you are going to share data or keep it proprietary.

[Slide.]

The next issue is clinical safety. Again, we have what we call kick-up factors. Here, across the top, it is level of manipulation, whether it is used for homologous or non-homologous use, whether it is combined with drugs or devices, and whether it is for a metabolic use.

So, here, basically, if you are something without any of the kick-up factors, then you don't have to do anything and you don't have to give us anything. If you are principally for local or structural reconstruction and repair but you have one or more of the

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kick-up factors, then you have to gather safety and effectiveness data.

But the application standard--what I am trying to get across here and I don't think I do it very well yet--but the point is that since it is for local or structural, what we do is we are looking at a part of the body. We are not necessarily looking at all the parts of the body.

So the level of testing necessary might be lower because it doesn't have metabolic impact throughout your entire body and that has to be taken into account here.

Finally, if it is for reproductive or metabolic use and it has the kick-up factors, again, you are going to have to gather safety and effectiveness data. There will be, again, an application with a standard similar to drugs or biologics taking into account the fact that it does have an impact on your entire body.

[Slide.]

With respect to claims, if it is surgery, we don't want to control the surgeons. "It works in my hands." So we aren't going to control the claims surgeons make. There is no industry action and no requirement to the FDA. For all others, we are going to try and get a handle on some of the claims.

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The claims that were being made in some areas were quite truly utrageous. What we are going to do is we are going to say, look, everybody has got to have clear, accurate, balanced and not misleading labeling. If you are an entity that otherwise doesn't have to have a regulatory submission, you are not going to need a regulatory submission just for your labeling.

So some of you will not have any submissions to the FDA whatsoever in any substantive area. However, if you are filing an application with the FDA, because of a kick-up in one of the preceding slides, then the normal rules for labeling apply, that there be clear, accurate, balanced and not misleading labeling.

[Slide.]

Finally, the baseline knowledge of industry; again, surgery, no industry action and no regulatory submission. But for all others, and I do mean all, interstate, intrastate, most complex, least complex, everybody is going to be required to register and list with the FDA.

We are not going to put that into effect until and unless we can develop a very simple electronic submission form, something where we will be able to have you do something as simple as, and this isn't necessarily what we will do, but go to the FDA's World Wide Web page

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and download an application form, an registration and listing form from our webpage, fill it out, press a button and send it in.

If you can't figure it out, there are a bunch of ten-year-olds around the country that can give you help. It will be very simple. It will be something that even, let's say, physicians in private practice doing reproductive work, will be able to do without a lot of trouble.

We, obviously, will have several different ways that people can come in to us but we decided it was essential for us to know who is doing what and also for you to have an opportunity to get on mailing lists or otherwise learn what we expect of you.

So that is the system in a nutshell. We are going to triage our inspections as well. We don't have a lot of extra resources for inspections. These will be field-drive inspections but, since we know we don't have a lot of extra resources, we are going to take seriously into account whether entities are accredited that will mean something in terms of us making decisions about when and how often to inspect.

We are still thinking about how to have some sort of random sampling or something so we have some kind of baseline of understanding of what is going on out

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there. You will be subject to inspection but it is not going to happen as often as it might in other industry areas.

So it is going to be very important to see whether industry can, in fact, meet these standards, live up to the expectations using other measures such as accrediting societies and the tort laws and the like to keep everybody on the straight and narrow path.

Finally, a little bit about implementation. We want to hear from you today. We will be listening to you avidly today. And then we will leave the docket open and you can write in comments. After we see whether this conceptual approach flies, we will then engage in notice and comment rulemaking.

Right now, we have a patchwork quilt of regulation. What we will do is use rulemaking to fill the holes in the quilt and to put in place this basic system so you will have another opportunity to comment on what we are doing and the particulars of it during the notice and comment rulemaking phase.

With that, the more subtle complexities of this will be handled by the moderators and the FDA speakers. We are going to, as your program indicates, divide up the day into different sections. So the moderators and the speakers will be able to present to you each of these

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areas in more detail and, obviously, we will be here to respond to your questions.

With that, let me turn it over to Jay Epstein who is going to be the first moderator.

General/Conventional Eye and Reproductive Tissue Therapies

DR. EPSTEIN: Good morning. As Mary said, I am Jay Epstein. I direct to Office of Blood Research and Review. I will be moderating our first discussion section which is on the general or conventional tissues which include, as you know, musculoskeletal, cardiovascular, ocular tissues, et cetera, and also reproductive tissue therapies.

Before we start on that session, however, I have been asked to provide a few of the housekeeping remarks. Let me first note that we do have a telephone number for incoming messages which is 301 443-2585. Let me also just mention that we have a consistent format throughout the day in each of our three discussion sessions.

We will have a brief overview trying to focus on some of the particulars of the regulatory scheme applicable to that set of products. We will then have opportunity for public discussion.

We have had requests for presentation and we have allotted time according to the number of request.

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Generally speaking, we would ask you to limit remarks to ten minutes and then provide five minutes for question and answer.

I would ask that every speaker state his or her name, affiliation and, for the record, to disclose whether that person is in the employ or has been in receipt of payment or travel reimbursement on the interest of any participating or interested party.

Let me say that if the discussions provide time at the end, we will permit those who have not specifically asked for time to make any additional comments that, of course, will be recognized by the Chairperson. During the presentations, we will also circulate cards on which questions can be written down. These will be brought up to the podium and, again, as time permits, they will be read and provide the basis for question and answer.

We do have our technical experts with us for each of the sessions and questions regarding the scheme can be addressed to those individuals or stated more generally to the podium.

As far as formal provision of comments, as you know, the scheme was published to the Federal Register and a docket number has been identified for comments. The docket number is 97N0068. We request that comments

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be sent to us by April 17 although comments received later may still be considered.

Now, before we launch, let me give special thanks to Marty Wells who had the lead role in organizing this workshop for us today. Ms. Wells is also going to be the first speaker in our introductory talks and she will outline how these requirements would play out for the conventional ocular and reproductive tissue therapies.

Marty?

FDA Introductions to the Issues

New Requirements for Tissues

MS. WELLS: Good morning. I would like to briefly describe, as Jay said, the changes that the proposed framework would have on the regulation of tissue for transplantation. Tissue for transplantation has been regulated by FDA since December of 1993 under an interim regulation.

I would just like to pull together for you, especially for the people who are here to approach only cellular therapies, what is new for tissue for transplantation and what we are extending for tissue for transplantation within the schema that is in your documents.

[Slide.]

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The tissues I am referring to are what we are currently calling conventional tissues which are the musculoskeletal tissues, bone, skin, tendons. Most of these are from cadaveric donors. Also ocular tissue, again, from cadaveric donors, cornea and sclera.

We are also including within this group the reproductive tissues and I will go into that a little bit more later in that these would be gametes, sperm, oocytes, zygotes and embryos. The majority of these fit the concepts in your documents of minimal manipulation and homologous use. I am not going to go into that more because you have those definitions.

[Slide.]

The communicable-disease requirements proposed in the new framework are based on what was originally in the interim rule for tissue for transplantation. It was, again, published in 1993. We have a final rule and it is completing the final stages of agency signoff. It only clarifies the interim.

I know that, at a different talk, I said that it was also completing the final signoff back in September, but we are committed to that and we hope that it will be soon.

The interim rule only addresses tissue for transplantation, as I said. It specifies requirements

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for donor screening and testing. These are for hepatitis B and C and for HIV. The donor screening is for risk factors. Again, these are specified under the interim rule and are mostly for cadaveric donors. Next of kin would provide this information.

It would, for instance, discuss issues of illegal drug use or certain sexual activities which would make these donors high-risk donors. It also requires certain things for written procedures and records. These were kept addressing specifically under the interim-only donor testing and screening to prevent communicable diseases and are provided for inspections and recall and destruction of tissues which were questioned or judged to be inadequate because either of their identification or the fact that donor testing and screening was not very well documented.

So, how does this proposed framework relate to tissue and what is new?

[Slide.]

Again, it reiterates the basic requirements necessary to distribute a safe tissue as we have defined it.

It also provides the basis for regulatory consistency for all human-derived tissues. This is based on potential risk to the public health. It proposes an elaboration on

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previous requirements. It specifically elaborates on donor testing and screening. Dr. Pereira will go into that in more detail.

And, for good tissue practices, it elaborates on issues such as written procedures and records. Again, these were issues that were in the interim rule and Dr. Solomon will speak to those.

[Slide.]

For tissues, the framework also proposes to add to the interim rule and the final rule requirements other regulatory requirements. These, as Mary has gone into them, I don't think that I will elaborate on them. If you have further questions on them, we can do that later. These are submissions of registration and listing.

This would be a form, as Mary said, a very simple form. It would include, also, a submission of a report of adverse events. These would be specifically related to transmission of infectious diseases. We are not interested in errant accidents which might occur during the processing or distribution phases.

Those will also be required but these are to be kept at the establishment in the event of inspection at that point. So we are not asking for any other submissions except for those two for this tissue class.

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Promotion and labeling requirements have been addressed within Mary's discussion. We are saying that for tissues, that general claims as a tissue are allowed but, in order to have other specific claims such as, for instance, they are safer, they are better, they have viral inactivation or they are sterile, a mechanism would be needed to substantiate these claims and that is something that we are open to suggestions and further discussion on.

Consideration for accrediting bodies and the relevance of industry standards for compliance efforts. These are some of the things that have been discussed at previous meetings we have had in the last couple of months. Reliance on accrediting bodies, as Mary said, for inspections would reduce our workload.

FDA is asking for specific comments on this from the different groups and how they view this concept and suggestions on how they would see it implemented by FDA.

[Slide.]

Finally, I would like to briefly discuss the rationale for inclusion of certain groups. We have proposed adding, as we have discussed, reproductive tissue. We are also proposing that we would add allograft heart valves to this schema under tissue and dura mater.

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This is based on long history of use. It is based on the fact that there is homologous function and also minimal manipulation for these products. We feel that disease control and processing control would be adequate to make sure that these products are safe.

Reproductive tissues are metabolic action, but it is localized. The recipient isn't immediately--it is not considered life-threatening if this therapy does not work. Also, I would just like to say that FDA is currently working with CDC as they implement the Fertility Success Rate Act which has given CDC the job to develop quality-assurance standards for embryo laboratories.

This is a voluntary effort. It will be a voluntary effort that, hopefully, the states will take over later on. But we are hoping to make sure that these are consistent with what FDA is looking for at this time.

Demineralized bone; because extraction of calcium from bone alters the tissue characteristics, it is seen as more than minimal manipulation. Based on this determination, FDA is proposing that demineralized bone be classified as the Class 1 exempt device. It would be exempt from premarket notification. It would be exempt from device GMPs and it would be required to follow the tissue standards for communicable-disease control and

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also for the good tissue practices which we will discuss a little bit more next.

We look forward to your comments on these issues. As Jay said, we have comments to the docket and we have comments--this is being transcribed. There is a notice back there as to where you can get the transcription if you require it and, hopefully, we will have a summary of the workshop later on in the next couple of months.

I think those are my comments.

DR. EPSTEIN: Thank you, Marty.

Our next introductory talk will be by Dr. Antonio Pereira who will describe the proposed communicable-disease controls.

Antonio?

Communicable Disease Controls

DR. PEREIRA: Good morning. Everybody has, as they say, the English and the other version. I am going to talk about Table 2 of the second, the proposed approach of regulation of cellular and tissue-based products.

[Slide.]

I would like to go through this table to clarify some points and maybe to tell you something more about the specifics and rationale behind all these decisions.

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[Slide.]

The question here and the concern is how can the transmission of communicable diseases be presented. Of course, because of our present technology, this will have to be focused on the donor.

[Slide.]

The donor will be tested for infectious-disease agents and will also be screened for infectious-disease risk factors.

[Slide.]

Testing will be for all autologous banked tissue, allogeneic nonviable tissue and allogeneic viable tissue.

[Slide.]

The rationale for testing autologous banked tissue, one of the main ones is protection of laboratory personnel and healthcare workers by identifying biohazards. Although these tests are only going to be recommended for autologous banked tissue, labeling as tested, and positive as tested and negative, or not tested, will be required.

[Slide.]

Under this, we will have, probably stem cells. The testing will be recommended for HIV, hepatitis, CMV viruses and the human t-cell lymphotrophic virus. In

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other autologous tissue, the testing will be recommended for HIV and hepatitis CMV viruses.

[Slide.]

This differentiation between viable and nonviable, as stated before, is because live cells, for example, leukocytes, can transmit particular infectious-disease agents just like the human t-cell lymphotrophic virus and cytomegalo virus.

[Slide.]

Allogeneic nonviable tissue, the testing will be required for HIV, hepatitis B and C virus and Treponema pallidum.

[Slide.]

Viable tissue will be required to be tested for HIV, hepatitis B and C viruses, the human t-cell lymphotrophic virus, cytomegalo virus and Treponema pallidum.

[Slide.]

But I repeat that requirements for testing for human t-cell lymphotrophic virus and cytomegalo virus would only apply to leukocyte-rich tissues.

[Slide.]

Under allogeneic viable tissue, we can also find the reproductive tissue. Reproductive tissue, including directed donors, will be required to be tested for HIV,

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hepatitis B and C virus, HTLV and CMV, Treponema pallidum and, additionally, for Chlamydia trachomatis and Neisseria gonorrhea.

Reproductive tissue from sexually active partners, intimate partners, will be only recommended to be tested as a bulk.

[Slide.]

For screening; high-risk behavior for HIV and hepatitis will be required for all cellular and tissue-based products except for autologous banked tissue and reproductive tissue from sexual intimate partners.

[Slide.]

Screening for Creutzfelt-Jakob disease will be required for all allogeneic tissue, viable or nonviable, except, as before, for reproductive tissue from sexually intimate partners and autologous tissue. In addition to screening, a gross and histological examination of the brain will be required for dura mater donors.

[Slide.]

Screening for tuberculosis will be required for all allogeneic tissue, viable or nonviable, except, as before, for reproductive tissue from sexually intimate partners and autologous banked tissue.

The table is a little complicated. I will try to explain a little more about quarantine, for example.

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Quarantine for six months, pending retest of a living donor, will be required for all reproductive tissue that can be stored--for example, sperm--except for sexually active intimate partners.

It will be recommended for all allogeneic tissue from living donors that can be stored.

[Slide.]

This little fine print in all this notes what may be need to be clarified. For example, tissue from a donor that tests positive for any infectious-disease agent and/or has a positive risk factor will be considered not suitable for transplantation.

[Slide.]

However, banked tissue for autologous use, allogeneic tissue from family-related donors, reproductive tissue from sexually intimate partners or directed donors or cases or urgent medical need--for example, that is very rare, life-and-death situations, rare as to compatibility matches--will not be required to be destroyed if they are labeling biohazard or not tested for biohazards, as indicated.

[Slide.]

For autologous banked tissue that has to be labeled for autologous use only. If there is written advance consent of the recipient and it is documented and

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there is documented knowledge on authorization of the recipient's physician.

[Slide.]

The rationale for this, as stated by Ms. Pendergast, is the agency will not intervene with the decisions between a family and their physician and the agency would not intervene with the decisions between sexually active partners and their physicians.

[Slide.]

In summary, this is a proposed approach for infectious-disease testing. It is based on guidelines and recommendations previously addressed by the agency. I think it is based on actual guidelines followed at present by industry. It is, of course, pending discussion and comment from you. That is why we are here today.

Thank you very much. I will leave Dr. Solomon to talk a little bit more about the good tissue practices.

Processing Controls/Good Tissue Practices

DR. SOLOMON: Good morning.

[Slide.]

Referring to Table 1 in the handout, Dr. Pereira has taken you through Row A of Table 1 which is our product concern for the transmission of communicable

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disease. I am going to be concentrating on Row 2 of Table 1 in which our product concern is the control of processing.

As with the five product concerns, control of processing will depend upon certain product characteristics or product factors. These have been subdivided into three groups going from the least risky to the most risky. For instance, the least risk, as was mentioned before, surgery, cells or tissues that are removed and transplanted back into the same person in a single surgical procedure.

[Slide.]

Then, for the next two groupings of products, we have identified four product factors or attributes. These are manipulation, homologous or non-homologous use, the presence or absence of a non-cell or non-tissue component and whether the function is structural or reproductive or metabolic.

These same four attributes are taken into consideration for Row B which is the control of processing and, also, for Row C which is clinical safety and clinical effectiveness. Dr. Noguchi will be talking about Row C and he will be going into more detail on the four product factors or attributes.

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So I will not be saying anything additional on that.

The second group of products are really the ones that conventional tissue and reproductive tissue would probably fall into, and that is minimal manipulation, homologous use, there is no non-cell or non-tissue component and the product has a structural or reproductive function.

The next group which we feel has more risk has more than minimal manipulation. A non-homologous may have a component that is non-cellular, non-tissue, and is for metabolic function with some exceptions. Having divided the products into these three groups, we can now tell you the industry action required and whether or not there is a regulatory submission which will vary with the risk.

For instance, for products in Group 1, there will be no industry action required and no regulatory submission. For products in Group 2, which I will be focussing on today, we will require what are going to be called good tissue practices. However, there will be no FDA application.

Products in Group 3, in terms of what processing controls we would like to see for them, they will require good manufacturing practices that will be elucidated in

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that application to FDA and will be relevant to the product.

Some of these GMPs have already been codified. For instance, for a biologic product, you would follow the drug reg for GMP in the 211s and a device product would follow the A20s.

[Slide.]

In the next slide, I have tried to come up with a definition of good tissue practice. Again, this refers to the products in B2 on the chart. By good tissue practice, we mean the processing and handling procedures aimed, and I could put the word "only" in there--aimed only at preventing contamination and preserving integrity and function of the cellular and tissue-based product.

Thus, the GTPs are restricted to just those concerns. Process and handling procedures and controls aimed at providing the assurance of clinical safety and effectiveness--that is, those in the products for group B3--would include the GTPs but would not be restricted to just the above.

And these would be more inclusive controls and we are calling them GMPs.

Just some general statements on good tissue practices. We realize that many of the organizations have already published standards that include processing

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controls. We are not trying to, in any way, interfere with those but we, in our promulgation of good tissue practice requirements, we are trying to establish minimal baseline requirements and provide consistency across all products.

We would attempt to make these GTPs general in nature. In other words, we would be telling you what to do but not how to do it because we realize that that would vary with the size and complexity of your organizations and your own needs.

We would attempt to make these GTPs flexible; that is, if your operation does not perform certain functions for which we have set forth GTP requirements, you would not be expected to follow those GTPs.

To give you an example. If your processing does not involve the use of large equipment which would need to be disinfected between samples but, rather, let's say your processing involves disposable supplies. Then, logically, you would not be required to follow the good tissue practices that addressed equipment, cleaning and sanitation and those types of GTPs.

The approach that we are planning to take is a quality-assurance approach. I will say more about that in a minute. And then, as I mentioned before, there

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would be no FDA application regarding simply the GTPs, themselves.

[Slide.]

As I mentioned before, industry has already put forth and published certain standards that include processing standards. If I have left anybody out, I apologize. In the past, we have looked at the industry standards and will continue to look at them for guidance to us as to what specifically should be required in a GTP.

[Slide.]

Now I am just going to quickly mention some possible requirements that might be addressed under good tissue practices. Time does not permit me to go into much detail on any of these, but they should all look familiar to you because these are included in industry standards today.

The first would be, as I mentioned, having a quality-assurance program that would coordinate and monitor all of your activities and make sure that you were doing things correctly, periodically audit the processes and, if mistakes were made, the quality-assurance program would investigate the mistake and possibly make sure that corrective action was taken if appropriate.

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Then, the next main subject might be we would expect you to have some sort of general organization and requirements for qualifications of your personnel. Again, all of these are going to be directed toward preventing the transmission of communicable disease, preventing contamination and preserving integrity and function of the product.

The next facilities, for instance, would be aimed at having appropriate space and a clean environment to do the work, equipment, supplies and reagents. As I mentioned before, you would want to qualify and maintain and disinfect your equipment if you used equipment that came into contact with multiple samples.

Under process controls, we would expect you to have written procedures that covered all aspects of your operation. I wanted to mention that some of these requirements are already in the interim rule and the soon to be published final rule although we did not specifically call them good tissue practices.

For instance, this one coming up, written procedures as well as general and specific record keeping which could be considered GTPs are already in the interim and final rule.

So we would expect written procedures, some kind of tissue identification, some kind of mechanisms when

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there was a change in the process, to make sure that the change was working correctly and that it had been approved. And then there would be requirements for the quarantine of tissue, as Dr. Pereira mentioned, and also for the release from quarantine.

In other words, do you have appropriate release criteria, have they been reviewed prior to release of the product. We would also like to see labeling process controls; in other words, have the labeling procedures been verified as to the accuracy and integrity of the label.

[Slide.]

The GTPs might also include the following topics; for instance, holding and distribution. We would want you to define storage conditions such as temperature and the maximum storage period. Under distribution, we would want you to keep records of where you sent your tissue to and also is the packaging of the tissue adequate to insure the integrity of the product.

The next one, record maintenance. As I mentioned, that is already in the interim and final rule. And we would address who has to maintain the records, how long do they have to be maintained, are they secure, and would they be available for inspection by FDA.

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A new concept that we may introduce is that one of tissue tracking; that is, the ability to track the product from the donor source to the consignee that is the recipient institution or the final distribution, disposition of the product.

Then the last three, errors and accidents, transmission of communicable disease and complaint files. We are still discussing which of these factors you would just need to keep on file at your place and which you would actually have to submit a report to FDA. We would certainly want you to, at a minimum, keep account of errors and accidents, were they investigated, were they documented, was corrective action taken.

Those could be reviewed on inspection for transmission of communicable diseases. Again, if there is a documented case of transmission attributable to the tissue, we would expect you to keep records of that and probably notify is as well.

And then, also, at your site, you would have a file for keeping any complaints or what is often referred to as an adverse-reaction file which, again, would be accessible to review by an FDA inspector.

[Slide.]

Lastly, in summary, this looks very much like Dr. Pereira's last slide because I stole it from him.

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But, in summary, we are saying that what we are proposing today is just a proposed approach, that the GTPs that we intend to put forth are really based on an expansion of the GTPs that are already in the interim and final rule; that is, keeping written procedures for donor screening and testing and record-keeping requirements for donor screening and testing.

We would hope that whatever GTPs we come up with would be consistent with the already existing industry standards for processing. Lastly, we welcome your input on the subject and, again, you will have many opportunities to comment on what we put forth.

Thank you.

DR. EPSTEIN: Thank you very much, Ruth. We are ten minutes late, but we are scheduled for a break. I think a break is in the best interest of the group especially so Ruth can get a little bit of tea.

I would ask, please, to limit it to 15 minutes and to return no later than twenty of 10:00.

[Break.]

Public Presentations

DR. EPSTEIN: I would like to begin the public presentations. If time permits, at the end, we can have additional presentations or discussion.

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Let me first call on Gerald Cole. Again, let me remind each presenter to identify affiliation and any financial backing related to this meeting such as travel reimbursement.

If you would like to come to the podium, you are certainly welcome.

MR. COLE: Good morning. My name is Gerald Cole. I am Executive Vice President of Tissue Banks International TBI is a non-profit organization of eye and tissue banks with 26 locations across the United States. TBI and tissue banks have a long history of service to the medical community dating back to 1962.

TBI also helps establish eye banks throughout the world with 39 international eye banks associated with our international outreach program. Tissues provided by the TBI network in the United States include corneal and other ocular tissues, allograft skin, musculoskeletal tissues and other human allograft tissues for transplantation.

TBI has reviewed the FDA's proposed regulatory framework for banked human tissue. The underlying concept of differing levels of regulatory oversight, for differing levels of complexity associated with allograft tissue, is a welcome response to our needs.

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Much of the tissue community has been calling for a regulatory approach to traditional tissue-banking activities to match our long history of safe, effective service to those in need.

On the whole, TBI does not view the proposed framework with great concern. But, as we reflect back to 1993, neither were we overly concerned with the written word of the interim final rule. It was only later, during the interpretation and application of the interim rule, primarily in the form of FDA guidance documents, the problems manifested themselves in the form of issues like hemodilution, medical social history screening, hepatitis B confirmatory tests, tatoos and needle sticks, to name a few.

In our opinion, the eye and tissue banking community has adjusted and complied with the changes brought about by the 1993 interim final rule but not without some negative side effects. Within TBI, we estimate our overall technical and laboratory operating expenses to have increased 20 percent, drawing from resources typically devoted to donor outreach and other programs.

TBI has also experienced flat to lower donor volumes particularly the number of critically needed younger donors at some of our eye and tissue banks. We

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attribute this, in part, to the impact of the 1993 interim final rule. This comes at the same time the medical community is calling for more, not less, of certain allograft tissues.

While TBI experienced an increase in the number of donors declined in the screening process, we found no significant changes in the percentage of positive serology results and reported adverse reactions. In combination, TBI experienced flat to lower donor volumes, higher operating expenses and no measurable improvement in the safety of our service.

At the same time, another arm of the Health and Human Services and HCFA seek to lower healthcare costs in the United States. Unlike the 1993 interim final rule where there was concern about unsafe imported tissue and potentially inadequate donor screening, this proposed framework is put forward without any accompanying expressions of such concern over other tissue banking activities.

So, as the eye and tissue banking community is asked to consider additional regulation, the FDA must understand our hesitancy to readily support additional oversight over traditional tissue-banking activities.

We anticipate that any difficulties with the proposed regulatory framework would come not with the

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outline but with the dissemination of the details and its implementation.

At this point in time, we would like to address some issues associated with the proposed regulatory approach that may become areas of concern. The determination of what constitutes "more than minimal manipulation" will be vitally important to every tissue currently provided.

The criteria of homologous use could prove problematic depending on how narrowly or broadly this is interpreted. It is unclear if the FDA is asking the eye and tissue-banking community to dictate prescribed use of allograft tissue which has largely been determined by the medical and surgical community.

The scope and composition of good tissue practices is not clear at this point but has the potential to be the area of greatest concern depending on the extent of any additional requirements.

The determination of minimal manipulation and homologous use would apparently impact FDA's view of an allograft's clinical safety or effectiveness. This brings into question the ability to continue to provide tissues generally acceptable to the medical community that may fall into this category.

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In an effort to provide a regulatory framework for new techniques and applications of biotechnology, a unified approach for both conventional and new tissue applications may be unnecessarily burdensome on the traditional eye and tissue banking community.

FDA's willingness to share their proposed approach in this forum is commendable in that it offers an opportunity for dialogue and the exchange of ideas. We look forward to receiving more details of the FDA's proposed approach to the regulation of allograft tissue so the potential impact can be determined with greater certainty.

Only at that time do we feel a real consensus can be reached for an effective regulatory approach for human and allograft tissue.

Thank you for the opportunity to express our views.

DR. EPSTEIN: Thank you, Mr. Cole.

Any comments from the panelists?

Mr. Cole, do you have an example where you feel that FDA's definition of homologous use or minimal manipulation would cause any undue regulation of the conventional tissue?

MR. COLE: I think within our discussions there is a lot of different uses for fascialata. In

neurosurgery and ophthalmology and such, those were brought up by our group.

DR. SIEGEL: I would encourage you and other interested parties in providing through the docket or communications with us, lists of uses and manipulations that you may consider on the edge.

We have done our best to imagine such things in trying to figure out how and where we would draw the line, but where there are questions and where there are concerns about how the proposed policy might apply, having on record for our consideration those things and for our discussion with you, I think it would be very useful.

MR. COLE: I think we would like to do that. I guess it is not entirely clear, at least to me, when that process might start. It would certainly be great to start today. We can come up with a list and go over it with you before anything might be put out in the Federal Register, and if that is available right now, you might hear from us very soon.

MS. NORTON: Yes, I would like to second that because those are precisely the kind of issues that the Tissue Reference Group is going to have to come to grips with, and the more specific examples of where problem areas arise, the more that you can provide to us, the

greater will be the ability to figure out how to draw the lines, and I think as I said in the morning in my introductory remarks, ultimately, in some of these jurisdictional areas, we get down to very fine line drawing.

I know there are concerns about confidentiality when you are really describing a particular product and maybe an innovative product, but to the degree that you feel that you can provide specific examples, that would be enormously useful.

Thank you.

MR. COLE: Ms. Norton, does that mean that process starts now, today?

MS. NORTON: Sure, absolutely.

MR. COLE: That resource group is in effect?

MS. NORTON: Yes, the resource group is already in effect, and we are trying to begin to work on what our processes ought to be, as well as the substantive questions that will come to us, so we would like to hear from you on both counts.

DR. EPSTEIN: Thank you. I will next call on Richard Davey.

DR. DAVEY: Thank you. I am Richard Davey. I am Chief Medical Officer of the American Red Cross. I

fully expect the Red Cross to pay for my parking this morning.

I would like to thank you and the FDA for the opportunity to present the following statement at this important public hearing.

I am speaking on behalf of the Biomedical and Tissue Services. That is a division of the Red Cross that has responsibility for stem cells, both peripheral and cord blood, as well as banked human tissue. Therefore, I am going to comment on the entire document even though this session is focusing on tissue.

The Red Cross welcomes the opportunity to comment today on the proposed approach to regulation of cellular and tissue-based products. The proposed approach represents a significant effort by the Food and Drug Administration in cooperation with many individuals, companies, and trade and professional organizations to develop a comprehensive strategy for the regulation of human tissue.

More significantly, it represents a paradigm shift by the agency to avoid proscriptively regulating all aspects of certain products without regard for their safety record or use over the years. It also recognizes that we are all responsible for the delivery of safe and effective products, manufacturers and FDA alike.

The FDA has proposed a regulatory framework that takes a tiered approach to tissue regulation as we have heard this morning. The strategy addresses three priorities: one, the prevention of the use of contaminated tissues through infectious disease testing; two, the assurance of appropriate handling and processing of tissues; three, the assurance that clinical safety and effectiveness is demonstrated in highly processed tissues, tissues that are used for purposes other than their normal function, combination products, and products used for metabolic purposes.

The Red Cross appreciates the work that the FDA has put into developing the draft and coordinating with the many diverse regulated communities. The Red Cross concurs that the three priorities identified by the FDA are indeed the right ones.

The Red Cross supports the tiered approach to tissue regulation, however, we believe that tissue is a unique material and the regulation should recognize its uniqueness. We are concerned that the proposal to overlay existing device and biologic regulations to regulate composite tissue will lead to confusion, making compliance difficult.

The Red Cross encourages FDA to develop regulations specific to tissue, additionally, to

encourage consistency in regulation, we urge FDA to select one center to be the focal point for all regulations affecting human tissue.

We have identified four areas in the draft document that require specific clarification or comment.

Point 1. The Red Cross opposes the classification of demineralized bone as a Class I exempt medical device. The uses and safety record for demineralized bone are well established and there have been no adverse effects that warrant the more stringent regulatory classification as a medical device. Demineralized bone is a tissue and should be regulated as tissue.

The FDA has already extensively reviewed the process used to prepare demineralized bone. Indeed, the FDA is already on record stating in a June 17th, 1995, letter concerning the Red Cross product Grafton that demineralized bone is banked human tissue.

The FDA's sound conclusion was based on a recognition that demineralized bone was not processed beyond disinfection and preservation. In essence, the FDA correctly distinguished between processing that removes elements that would interfere with the therapeutic performance of a tissue, and processing which

adds elements to further enhance functions or characteristics.

Therefore, the Red Cross urges FDA to reaffirm their previous position regarding demineralized bone as tissue rather than classify this material as a Class I exempt medical device.

Point 2. The Red Cross supports FDA's decision not to regulate cord blood used autologously or in close family relatives. We agree that minimal regulation is required for these categories assuming all recommended infectious disease screening tests have been completed.

However, the Red Cross believes that cord blood that is not being used autologously or for close family relatives warrants closer regulatory scrutiny since disease transmission, processing methods, and effective therapies are of major concern.

Therefore, the Red Cross supports FDA's decision to regulate cord blood according to its intended use. We strongly support FDA's more stringent regulatory approach for allogeneic cord blood.

Although FDA acknowledges the distinction between these two categories, the specific regulatory reference could be more clear. The Red Cross believes that the regulatory reference to allogeneic cord blood is in Table 1, Section C(d)3. This requires that products

with metabolic use, if not used autologously or in a close family member, requires studies under an IND and a marketing application submitted under a BLA.

Point 3. The FDA in meetings held from November 1996 through February 1997 emphasized its reliance on industry consensus standards for processing controls and product standards. However, there is only a brief reference to industry consensus standards on page 25 of the draft document.

The Red Cross believes that there is great value in the use of industry consensus standards and encourages FDA to emphasize the involvement or professional groups in the development of standards.

We believe that developing standards is a joint role and responsibility where both FDA and industry have their strengths. By using industry consensus standards, the FDA will benefit from broad acceptance of the standards within the regulated community since most outstanding issues are usually resolved during the standards development process.

The Red Cross also believes that there is significant value in certification by professional associations. Similarly, we support and are encouraged by FDA's willingness to issue licenses based on a certification that standards have been met.

The Red Cross believes, however, that FDA should be actively involved to ensure that the certification process is sufficiently rigorous and should be prepared to take action in the case that a company fails to meet certification standards.

Point 4. The role of the Tissue Reference Group in making jurisdictional decisions and applying consistent policy is unclear. The FDA states that scientific or regulatory issues would be resolved "expeditiously" through the involvement of the Tissue Reference Group.

The structure and functions of this important group are not well defined in the draft document. FDA states that the Tissue Reference Group will provide a "single reference point for all tissue-related questions received by the Centers or the Office of the Chief Mediator and Ombudsman."

The Red Cross requests clarification about the role of this new group in relation to the role of the Office of the Chief Mediator and Ombudsman, whose role it has been traditionally to resolve jurisdictional issues among the Centers.

The Red Cross supports the concept of the Tissue Reference Group, however, we believe the FDA should establish clear standard operating procedures for the

group including mechanisms which ensure decisions are made "expeditiously" and are communicated to industry in a clear and effective way.

In conclusion, we thank FDA for the work that went into the development of this proposed regulatory approach. As I have discussed, the Red Cross has significant concerns about the proposed treatment of demineralized bone and requests clarification of several areas in the draft document. However, we support the major features of the proposed regulation especially the tiered approach to the regulatory process.

The American Red Cross appreciates the opportunity to comment today and looks forward to working with the FDA and others in implementing this regulatory strategy.

Thank you.

DR. EPSTEIN: Thank you, Rick.

I guess I will toss out the first question. With respect to demineralized bone, is it your opinion that we are dealing with a process which is not more than minimal or simply that we have a track record for a product that is not raising current concerns, because the issue of the determination as a tissue under the interim rule was different because there was not degree of processing as a criterion in the interim rule, and

although we might concur on a conclusion that there is a clinical track record, the question pointedly is whether that is because it is only minimally processed or not, and that is really the point of distinction as far as the framework is concerned.

So, could you comment on that.

DR. DAVEY: I will do my best. I think our position is that indeed it is a minimally manipulated product. It is a product derived from bone, used to repair bone, and the process involved, as I mentioned, involves removing or manipulating the product to remove products that might impair its therapeutic effectiveness, not add, change, or enhance its characteristics.

Therefore, since the record is safe, Jay, the record is long and safe, we feel the process is minimally manipulative and doesn't warrant the more stringent regulation that has been proposed.

If any of my colleagues from the tissue area would like to expand on that, I would welcome it. Yes, Mary.

MS. PENDERGAST: I could just make a comment. This kind of product is the poster child for other parts of the industry that say that this is the paradigm of the highly manipulated tissue, and they should be treated like however you are treating them.

So I would be curious for those of you who believe that to please respond to that challenge that this is really just minimal manipulation today, and get that out on the table

Thank you.

DR. EPSTEIN: Amanda.

MS. NORTON: Yes, I just wanted to say to Dr. Davey that I couldn't agree with you more about our need, and the purpose of the Tissue Reference Group is because we anticipate a lot of highly specialized jurisdictional questions, I think as Gerald Cole pointed out, on the question of what does "minimally manipulated" mean, what is a nonhomologous use, and this is not separate from, but sort of a specialized group that will work within.

Obviously, the Part III regs are there and can be used. What we are trying to do, and we hope to hear directly suggestions from you, is provide a mechanism that both helps answer the questions as we go into this area, as well as provide the kind of responses that you need in the more formal way through the Part III process.

So we do expect, one, to have one decisionmaking process ultimately. How we run it internally in responding to being expeditious and meeting your needs is part of the reason why we really are soliciting your comments today.

So, we do not disagree with you, we don't disagree with what Gerald Cole said. We are looking for suggestions and advice. Obviously, we have a process well set up now that has worked pretty well for the other kinds of areas that we have dealt with, but I think there are some novel questions here, and that is why we have the Tissue Reference Group with its expertise both in the jurisdictional area, as well as the scientific area.

DR. EPSTEIN: Dr. Zoon.

DR. ZOON: Thank you, Dr. Davey. I just wanted to make one quick point of clarification. While demineralized bone is considered under this schema as a Class I device, the oversight and regulation required would be the same as any other tissue, and I just wanted to make sure there was no misunderstanding as to the level or the scope of information and regulation that the agency would be asking.

I think we tried, just so you know, that to take various products and objectively put them through the schema, and then try to look at the history related to those products to weigh in on where they would fit, but we appreciate your comments and will look forward to additional comments.

DR. DAVEY: Thank you, Dr. Zoon.

DR. EPSTEIN: Any other comments from the panel? Antonio.

DR. PEREIRA: Yes. It was mentioned before that there was a decrease of the flat number of young donors after the screening test. Has the American Red Cross felt the same thing?

DR. DAVEY: Screening for?

DR. PEREIRA: A decrease in the number of young donors after screening questions.

DR. DAVEY: Tissue donors.

DR. PEREIRA: Yes.

DR. DAVEY: Randy, could you maybe answer that?

MR. MAY: I am Randy May, COO of Red Cross Tissue Services. We have noticed a decrease in donors, but it is a smaller percentage of the pool we are looking at, and the recent enforcement of the rules to date have decreased the percentage of the initial donors that were screened that we can obtain.

I don't have off the top of my head that broken down by age group, so I can't affirm or deny Mr. Cole's argument about the younger donors.

DR. EPSTEIN: Thank you. Thank you, Dr. Davey.

We will move on then. I would like to invite Jur Strobos for comments.

DR. STROBOSDANNE: Good morning. My name is Jur Strobos. I am anticipating that I will be paid by Biocoll Laboratories on whose behalf I am here today.

We appreciate the opportunity to provide a response to FDA's proposed approach. We intend to supplement our remarks in particular with some more detailed information about collagen.

Our comments today largely are going to relate to the concepts of minimal or more than minimal for which I am using the concept of extensive, and we would like to note that this tiered approach may actually fail if things that fall just on one side in the more than minimal are not handled appropriately and flexibly.

I think that is our biggest concern and I think our second concern has to do with collagen.

That said, I would like to address three issues. One is relating to standards of effectiveness that would be applied by FDA to structural human tissues that might be more than minimally modified.

The second is the application of devise good manufacturing practices to the same product category.

The third is a request that FDA consider fulfilling its promise with regard to lowering the level of regulation when standardized treatments of a human tissue don't affect pertinent characteristics by

considering reclassification of standard acid wash of human connective tissues as minimal manipulation.

That is also sort of consistent with the concept mentioned earlier that many of these tissues that are used broadly and therefore identifying indications, as the discussion with Dr. Siegel was earlier difficult.

Let me introduce Biocoll Laboratories. The company intends to become a leading developer and supplier of bone regeneration materials. We work with human tissue banks in the processing and marketing of acellular structural tissues. We conduct research on processing methods to ensure that our banked human tissues are uniform and consistent, and it is a small, start-up company with less than 20 employees.

We work closely with a number of academic institutions, and the corporate intention is to develop new standards for quality for banked human tissues by investigating the scientific underpinnings of new and current processing.

That said, I think this company is particularly challenged, therefore, by the concern that classification is more than minimally processed will incur an extent of regulation not commensurate with the change or modification in the processing.

Notwithstanding these concerns, we are highly supportive of the formal FDA initiative. For the last three and a half years since the near simultaneous publication of FDA's somatic cell policy and the interim human tissue regulations, I think the private sector has been buffeted by uncertainty.

Policies have been issued in various forms from guidances to speeches, from letters to specific manufacturers, to notices of open meetings, the net result of which has made consideration and planning for regulatory issues complex and unpredictable.

There has been I think inconsistent advice, and I think confusion has ridden in part because of complexities in the next technology and their application to this new field, and in part because the field is somewhat novel to FDA, as Dr. Siegel earlier noted.

We think that FDA's approach is thoughtful and thorough, and we congratulate you on a plan that synthesizes such diverse fields as cellular therapy, storage of cord blood bioengineered to human tissue, and banked human bone.

As noted, our concerns focus on a narrow part of the spectrum today, the transition from banked human tissue, minimally manipulated acellular structural tissue to more extensively manipulated tissues intended for use

for local structural reconstruction or repair, the homologous tissue use proposed to be regulated as a device.

On Table 1 in FDA's handout, these transitions are found between B2 and B3, and C1 and C2.

With regard to clinical safety and effectiveness, we applaud the stated intention to permit the use of historic surrogate endpoints that have long been used by the clinical community to establish the effectiveness of surgical interventions.

To that end we suggest, for instance, that bone production in osteogenesis as shown by X-ray or other modalities should be a satisfactory endpoint to demonstrate effectiveness of a human tissue material to substitute for an autograft or to be viewed as comparable to similar but less extensively processed allograft bone.

Furthermore, use of such a surrogate endpoint would ensure that clinical studies do not need to be uselessly performed in all of the vast array of clinical indications for which minimally processed bone allograft materials are currently used.

To that end, bone allograft can be used to fill bone cavities. It can be used to promote fusion. It can be used to grow bone where none is present. Of course, it can also be used to form new bone in places where a

diseased bone has been removed. The goal in all cases is osteogenesis and that should be the endpoint.

A more difficult question and one to which the proposed approach currently gives no answer is the appropriate selection of controls to the extent that there are clinical studies on more than minimally processed tissue.

Twenty years ago, FDA dealt successfully and creatively with the issues of improvement or modifications to pre-1976 devices like crafting the 510(k) program later codified by the Safe Medical Devices Act at 513(a) of the Food, Drug and Cosmetics Act.

The success of that program relied in its early years on an understanding within FDA that clinical data on grandfathered or predicate devices did not exist. Notwithstanding that lack of information, new entrants with slight modifications, those that would under the proposed approach be more than minimal, were not required to demonstrate the label of safety and effectiveness of the predicate device.

Instead, the agency exercised judgment, stepping away from the empiricism that is implicit in controlled clinical trials of efficacy and requiring that data submissions be commensurate with proposed changes.

Exercise of clinical judgment requires agency personnel to hypothesize about the effects of modifications and, in turn, to design clinical evaluations around those changes.

The requirements for the exercise of that judgment for nonhuman tissue-based medical devices has diminished over the last 20 years as the database on predicate products has increased. Now the average clinical reviewer can pull files on predicate devices which contain clinical or other information that serves as a basis for consideration of the new device.

Over time, therefore, the imposition of concurrent treatment controls for clinical data on new products makes sense, but it would not have made sense when the 510(k) program first began.

Under the proposed approach by FDA, more than minimal modification of human acellular structural tissue materials could be subject to the new clinical review standards developed in the last few years as the device program has properly matured. If this becomes a reality, and our experience suggests that it may already be the case, the agency will impose a barrier to slight modifications and innovation in the processing of human tissue that cannot be overcome. Such a barrier may be appropriate for major modifications, such as the

manufacture of bioengineered human tissue in which the question is whether one has, in fact, produced the relevant component of human tissue.

Further, the capital investment research and eventual premarket application approval that would follow with this marketing exclusivity and potential patent protection may be sufficient to permit such a company to go forward. That barrier is not appropriate for minor modifications in which the totality of the source material remains banked human tissue.

While the agency has proposed a two-tiered approach with minimal modifications on one side and more than minimal on the other, the reality is that modifications are a gradual gradient and the device program must tailor regulatory requirements to the scope of the modification.

I think a similar point can be made with regard to the difference between GTPs and GMPs. This is the jump from B2 to B3. While FDA has suggested the development of good tissue practices for minimally processed tissue, the gap between GTPs is defined today really and device GMPs is codified in Part A20 of 21 CFR is huge and substantial.

Under the proposed approach, any processing that is more than minimal for acellular structural tissue will

trigger the full imposition of device GMPs. This is unworkable. As stated, such an approach may be appropriate to major modifications, such as bioengineering of human structural tissue or a combination of manufactured implantable device with human tissue, less extensive modifications will be unable to meet device GMPs.

I need only, for instance, mention all the new design controls and the difficulty of trying to figure out the human body was designed and whether or not there are records relating to that.

The last issue I would like to raise is the issue of collagen, which is somewhat separate. In the proposed approach, FDA has stated that it intends as time goes on and additional information is generated about procedures, in the more than minimal manipulation category, the agency intends to consider them to be in the minimal manipulation category when clinical data and experience show that the procedure does not alter the biological characteristics of the cells of nonstructural tissue or the relevant structure-related characteristics of the structural tissue.

This flexibility will permit product processing that has been found not to affect the pertinent characteristics of the product to be subject to the lower

level of regulation. As part of the discussion earlier, this may be appropriate perhaps for DFDBA, demineralized freeze dried bone.

We suggest, however, that the time is ripe for such a decision with regard to minimally manipulated human connective tissues that are generally rich in type I collagen. This includes banked human bone, tendon, and cartilage.

The FDA has stated in its document that collagen has always been regulated as a device, and it states that the combination of collagen with human tissue is a device. I guess I would contest that. I think that, in fact, most human collagen is not regulated as a device. For instance, demineralized freeze dried bone is 90 percent type I collagen and a vast majority of other products that are currently regulated as banked human tissue primarily consist of minimally manipulated collagen.

The history of FDA regulation of collagen, I think deserves review to understand the origins of this inconsistency in FDA's current proposed approach. As is often stated, bad facts can result in bad law.

Minimally manipulated type I allograft human collagen has been transplanted from human to human for decades as the principal component of allograft bone and

allograft tendon transfers. These materials have not been subject to FDA regulation. They are currently banked human tissues.

In contrast, xenogenic and highly purified collagens have generally been subject to FDA premarket approval regulations. In 1981, FDA first approved a premarket application for Zyderm, which is noted in the labeling as both highly purified and xenogenic as it originates from calf skin.

Subsequently, FDA has also approved a premarket application for Zyplast and Keragen, which were even more highly manipulated with the addition of glutaraldehyde, an historic tanning agent to the processing.

These products are all indicated for use in the largely cosmetic management of skin defects. They contain not only type I, but also type III collagen.

Additionally, there are numerous other products with highly purified xenogeneic collagen including suture materials, absorbable hemostatic agents, bone paste, and urinary incontinence materials.

In the mid- to late eighties, concern was raised about possible development of autoimmune disease from subcutaneous bovine collagen injections. In part, this interest is stimulated by isolated case reports and in

part from the filing of product liability lawsuits against a particular corporation.

DR. EPSTEIN: Excuse me, but I need to ask you to try to conclude.

DR. STROBOS: Okay. I am almost done.

While the premarket studies have demonstrated the possibility of acute hypersensitivity to bovine proteins, no reports of induction of chronic autoimmune disease have been reported.

After several comprehensive studies, the agency concluded that, in fact, there was no evidence to support induction of autoimmune disease from bovine collagen. This history, despite its entirely benign outcome, has left the agency leery of collagen notwithstanding that the vast majority of the banked human tissues we are talking about today are nothing but collagen from heart valves to bone and tendon allograft.

If the agency intends to leave these minimally manipulated collagens regulated as human tissue and used homologously, it should take steps to be consistent with all human collagens that are minimally manipulated and used homologously. The science would certainly support such a decision.

I appreciate the opportunity to speak here today, and if there are any questions?

DR. EPSTEIN: Do we have any questions or comments from the panelists?

If I understand your remarks correctly, what you said is that there is a two-tiered system being proposed, but there is, in fact, a gradient of possibilities in processing as well as intended use, and you have suggested indirectly that a 510(k) model might have fit that situation better.

Can you explain what you would propose that we do for a more than minimally manipulated tissue, but which is, as you called it, close to the line?

DR. STROBOS: Well, I guess my suggestion is that the Tissue Reference Group should not be limited only to jurisdictional issues. My specific suggestion is that you need to have a body of individuals within the agency who not only evaluate whether or not something is minimally manipulated, but based on their assessment of what the more than minimal manipulation or modification is, they also make an assessment of what kind of data is required by the agency.

I understand under the current situation what you have is a circumstance where a jurisdictional decision is made, and then the issue is referred to individuals elsewhere in the agency who may not understand the basis for the jurisdictional decision, who

may not understand what parts of the modification it was that created the need for more data, and who may them impose inflexible requirements that come out of that division or center.

I think that one has to have a more coordinated approach, as it were, to not only the jurisdictional issues -- which the table is very good at -- but one also has to have a coordinated approach to what kind of data requirements the agency may need.

DR. EPSTEIN: Thank you. Any other comments from panelists? Amanda.

MS. NORTON: Yes. I would just like to say I think that is a useful comment in terms of the coordination aspect between the jurisdictional decision and the ultimate handling of the product by the agency.

That is something that we have been building into that process, and I think further thoughts on how to handle that is something that if others have suggestions, I think it is very important as we go forward on this to be able to sort of deal with borderlines.

Borderlines is where we have I think the most difficulty and can spend the most time, and as part of that, in fact, in other areas we have dealt with it by way of what kind of data are we really talking about,

what do we really need here, because not everything fits nicely into a regulatory scheme.

So I think it is helpful to identify that, as Dr. Strobos has, and I would encourage others who can bring issues like that to our attention to do so, so that we can anticipate them and do what we can to provide a structure and a process that will deal with them.

DR. EPSTEIN: Any other comments?

MS. WELLS: In your introductory remarks, you said something about acid wash and minimal manipulation?

DR. STROBOS: Acid wash, yes.

MS. WELLS: Can you elaborate?

DR. STROBOS: Well, there has been a standard treatment for connective tissues under which they are basically mildly acid washed, treated with a mild pepsin, and the connective tissue is solubilized and then used in a variety of circumstances. That has been historically used, as well, by surgeons, and I would anticipate that it will -- you know, it is an industrial process to a certain extent, and I think it needs to be considered minimally manipulated.

The agency has already evaluated a number of premarket applications in that area, and I think that we have a long record with regard to that, and if you look at the criteria that the agency has described as what

constitutes minimal manipulation, things like treatment with -- I mean lyophilization and treatment with acid, I think is consistent with that at least for human collagen.

I think the issues with regard to xenogeneic collagen, I think we all agree are very different.

DR. EPSTEIN: Any other comments from the panel? If not, we will move on. Thank you.

I would like to call on Mary Beth Dannefel.

MS. DANNEFEL: Good morning. I am Mary Beth Dannefel and I am representing today the Eye Bank Association of America as its chairperson.

The EBAA has reimbursed my travel expenses, but I would also like to disclose that I spent the night in the Lincoln bedroom.

I very much appreciate this opportunity to provide comment on the Food and Drug Administration's proposed approach to the regulation of cellular and tissue-based products. The EBAA was founded in 1961. It is a nonprofit organization of 112 member eye banks in over 150 locations.

Despite the semantics, our banks are not an industry, they are 501(c)(3) charitable organizations which maintain close ties with their local communities through their philanthropic activities.

In addition to providing corneas for transplantation, U.S. eye banks makes eyes available for education and research. Eye tissues are frequently provided gratis. This has greatly strengthened the research programs of educational institutions and has contributed to significant technological advances in the improvement and restoration of sight.

Eye banks voluntarily developed a system of self-regulation in 1980. That is more than 16 years ago. That year, the EBAA promulgated strict medical standards for eye banks and monitored compliance through an inspection and accreditation process.

Today, EBAA standards are mandatory for all active members. These standards are reviewed and revised semiannually and as often as necessary to ensure state-of-the-art practice in the laboratory setting.

Additionally, independent review of our standards is provided by the American Academy of Ophthalmology. EBAA medical standards were developed with the goal of providing safe corneal tissue suitable for transplantation. Over the years these standards have been refined and strengthened to the point that today's strict standards exclude or contraindicate the use of tissue from donors with clinical signs or a diagnosis of

any of the infectious diseases that the FDA sought to prevent in its 1993 interim rule.

The EBAA standards mandated HIV testing as early as 1985, hepatitis B testing in 1986, and hepatitis C in 1991. A mandatory adverse reaction reporting system monitors the results and corroborates that eye banking is a safe, effective system which does not pose a threat to public safety and does not present a problem that the FDA needs to fix.

We support appropriate oversight specific to eye tissue. We provide that. Our record is unsurpassed by any other form of tissue organ or blood used in transplantation. Clearly, the EBAA and the FDA share a common goal. We both seek to protect the public health to the greatest extent possible.

We appreciate the difficulty of the task at hand as we diligently worked in 1980 to establish appropriate medical standards for the eye banking community, not an easy task, by the way.

Incumbent in protecting the public health is the appropriate utilization of scarce health care dollars. As 501(c)(3) organizations, we understand and experience this challenge on a day-to-day operating basis.

The FDA matrix attempts to incorporate under one umbrella conventional transplantable tissue with that of

cellular and tissue-based products. At present, it offers a framework without the specificity that supporting guidelines and data might provide. It is the details which matter.

The cost of generic regulations required of the whole tissue community lacking tissue-specific standards is an inefficient use of governmental resources and unfairly taxes the not-for-profit system of eye banks.

The eye bank community represented through the Eye Bank Association of America cannot sign on to what is in effect a blank check. It is too costly for us to do so and may be too costly for the government to provide. The cost to the parties involved, both in terms of dollars as well as availability of eye tissue suitable for transplantation is just not known.

It simply does not make sense from a public health perspective, nor is it an efficient use of scarce resources. We strongly believe that the agency must meet two thresholds prior to adopting a regulatory program for banked human eyes: first, that a public health need be demonstrated; and second, that the solution is specific to the identified problem area.

Many here today will say that the EBAA program can fit neatly within the FDA program given that the present proposal outlines basic elements common to our

oversight program, and that it would not be any different for eye banks to correspondingly follow the FDA proposed standards.

This reasoning is flawed. Our experience with the 1993 interim final rule for the transmission of HIV and hepatitis can best illustrate this point. While the rule itself as printed in the Federal Register was generally workable to the communities regulated thereunder, the guidance documents drafted to enforce the rule were not.

Such guidance documents contain detailed requirements that were not scientifically relevant to eye banking practices, and yet, eye banks were held accountable to those requirements.

Eye banks must implement every practice in the interim final rule and all inspector guidance documents. We are doing so and unfortunately also witnessing an unnecessary loss of tissue suitable for transplantation.

Please remember our standing safety record, so we have to ask ourselves why we are discarding eye tissue from a nine-year-old donor whose only contraindication was pierced ears.

It should be understood and duly noted that tracking another regulatory construct and adhering to its documentation and testing requirements demands increased

staff time. While this may seem inconsequential to large businesses and for-profit ventures, incremental costs create a financial burden not easily offset in our not-for-profit banks.

At present, processing fees do not always cover the cost of eye corneal tissue procurement and distribution. Often, in many eye banks, charitable donations supplement the difference.

In effect, we will not only increase staff time to implement the FDA regulation, but also increase staff time and effort to raise contribution levels. Again, remember the eye banking community's safety record. We have to ask ourselves why we are spending unnecessary resources for no added benefit.

The Eye Bank Association of America does support registration for all entities engaged in the use of human tissue. We believe such registration will allow for full identification of the entire community and provide a vehicle for the transmission of information.

We again thank you for the opportunity to provide comment on the record and we would ask the FDA to consider us a partner in seeking to protect the public health and ensure the viability and maintenance of what is already a healthy eye banking system.

We respectfully ask you to reserve oversight until a need is demonstrated.

Thank you.

DR. EPSTEIN: Thank you. Do you have any comments?

MS. PENDERGAST: I have a couple of questions.

You mentioned active members. Do you have inactive members? If you are not active, what are you?

MS. DANNEFEL: In the process of applying, we have a category of a new member bank who is in the process of applying, and we have one eye bank in the United States that is not a member of the EBAA, but is licensed under Florida state law.

MS. PENDERGAST: Do your eye bank standards address infectious disease issues?

MS. DANNEFEL: Yes, they do.

MS. PENDERGAST: So you recognize that eyes can transmit infectious diseases?

MS. DANNEFEL: That is by history in the seventies and the eighties, and that was one of the reasons that led us to 1980 medical standards, to promulgating medical standards in 1980, before anyone else ever thought of it.

MS. PENDERGAST: Thanks.

DR. EPSTEIN: If I could pursue that point a little bit. You are arguing that because the products have been shown safe now, that there is no need for additional controls. However, these are the controls that we are advocating. We are simply moving them from the voluntary to the mandatory realm.

In other words, you would not argue against hepatitis screening or HIV screening, would you?

MS. DANNEFEL: No, we would not.

DR. EPSTEIN: So why do you object to it becoming a federal mandate?

MS. DANNEFEL: Well, under your proposed regulatory framework -- and I can refer you to a comparison table that we submitted to the FDA in early January -- our issue is with the GTPs primarily. I mean we are, of course, advocating screening and testing of donors to rule out infectious diseases.

What we are concerned with is the good tissue bank practices. Corneal tissue is an avascular allogeneic banked viable tissue. It is not batched. It is prepared one tissue at a time. It is very simply a process. We feel that the EBAA standards have already addressed the issues of infectious disease transmission and donor screening and that our safety record speaks for itself.

DR. EPSTEIN: Other comments from the panel?

MS. PENDERGAST: I have a question. We heard you when you said you don't want to have two sets of recordkeeping, one for your association and one for the feds.

Is there any other concern you have? I mean are you worried that your product liability or malpractice exposure increases by us making it a federal requirement as opposed to voluntary?

MS. DANNEFEL: Product liability, no. I don't think that has been an issue that we have expressed concerns about. Our experience really has to do primarily with the guidance documents. We recognize that the interim final rule already presented things that we were doing according to EBAA standards, but the application of the guidance documents impose some additional concerns in terms of individual inspection variation, variability, and issues like hemodilution review of donors in ear piercing and body piercing, and so on.

So, the real issue is with the details that haven't been specified in the GTPs.

MS. PENDERGAST: We issue, probably to some of your dismay, lots of guidances here at the FDA. If you would be so kind as to specify in a follow-up writing

exactly which guidances and exactly which aspect of which guidances you take substantive issue with, I would appreciate that very much.

MS. DANNEFEL: Under the interim final rule?

MS. PENDERGAST: Yes. Thanks.

MS. DANNEFEL: We would be happy to.

DR. ZOON: We recently have a new policy which is the good guidance practices in which there would be opportunity for comment on draft guidances before anything is made final. I would also say that if there are issues in terms of heterogeneity with respect to implementation of guidance practice inspections that have raised concerns, we would be very interested in hearing that, because the only way that we can look at these things and make corrections and react objectively is if you provide information into the agency for us to respond to.

So, I offer you an open invitation to submit your experiences to the docket, so that we can see the specifics of where the problems arise and develop procedures that might be necessary to help in the future.

MS. DANNEFEL: Thank you. We would be happy to do that.

DR. EPSTEIN: Amanda.

MS. NORTON: This may have been covered, but I think it would be, in terms of the submission you mentioned having made to the agency in January, but I think it is not clear in my mind whether you are saying you have a set of processes which substantively do not differ from what is being proposed and you are concerned about the compliance costs of FDA's regulatory scheme or whether they are recognizing that we haven't filled in all the details yet, or whether there are substantive differences.

I think if you could submit something to the record that clarifies that, it would simply help us deal with some of the issues you raise, as well as thinking about how we should go about managing it.

I mean it is that distinction between are you talking about one-time changes of your procedures to conform them to a federal system, are you talking about substantive differences where you substantively disagree with the agency about what we want, or is it a combination of both?

If you could separate those out, so that we could clearly see them, I think it would be helpful.

MS. DANNEFEL: We are concerned about the costs. Substantive differences, really it is difficult for us to assess because we don't have the details that you might

write into the GTPs. Until we see those, we really won't know if you are going to add something that is totally inappropriate to eye tissue.

MS. NORTON: Your standards, have they been submitted to the record?

MS. DANNEFEL: Yes, they have.

MS. NORTON: Good. Thank you.

DR. EPSTEIN: Martha.

MS. WELLS: Just for the record, the guidance document that I think that you refer to was the one that was originally put out for our inspectors after the interim regulation. Since that time, we have had several public meetings. We have had responses to the docket. We think that we have come to some consensus as to what the high-risk behavior questions should be.

AATB and some of the organ procurement agencies have come up with a standardized format for their donor screening which fit in with our concepts of what high-risk behavior questions need to be asked, and with the final rule we hope we will be also publishing a draft guidance document which again only gives our current thinking for these high-risk behaviors. It is not a regulation, but it gives you an idea of what we are looking for with these questions.

This will be based on comment that we had at a workshop over a year ago, and we think it is consistent with the thinking currently.

I just wanted to clarify that for the record and hope that that will clear things up.

MS. DANNEFEL: Thank you.

DR. EPSTEIN: Thank you and we will move on.

Let me ask whether there is a representative of the American Society for Reproductive Medicine who would like to speak at this time? I was advised that Robert Stillman will be late.

[No response.]

DR. EPSTEIN: All right. We will try to accommodate his remarks later in the day.

Let me then call on Randolph May.

DR. MAY: Good morning. My name is Randolph May. I am president of the American Association of Tissue Banks.

I am delighted to have the opportunity to appear here today and to convey the association's comments on what we all must agree is a thoughtful and thought-provoking document.

The American Association of Tissue Banks was formed in 1976 to help ensure that transplantable human tissues were safe, of uniform high quality, and were

supplied in quantities sufficient to meet the national need.

Today, AATB's membership numbers 900 individuals and 68 accredited tissue banks who are engaged in the recovery, processing, storage, and distribution of human tissue. The association publishes and enforces standards and detailed technical requirements directed to bring consistency to tissue banking activities.

The association conducts on-site inspections and accredits tissue banking establishments only after banks have demonstrated compliance with these standards and technical requirements.

Such accreditation is a prerequisite for an establishment's membership in AATB. AATB also certifies tissue banking personnel based on proficiency, knowledge, and understanding using independently validated examinations.

AATB examines candidates annually and has certified nearly 1,000 tissue bank specialists to date.

To help ensure an adequate supply of transplantable tissue, the association operates a voluntary national tissue network that relays requests for specific tissue allografts from transplant surgeons to AATB-accredited tissue banks that distribute those grafts.

AATB has long believed that FDA can and must play a crucial role in regulating human tissues to protect the public from the small but real risk of disease transmission and to be fully supported in concept FDA's promulgation in 1993 of the interim rule, whose content closely tracked AATB's own standards.

AATB was, however, disturbed by FDA's failure to provide prior opportunity to comment on the provisions of the interim rule, and is perplexed by its failure to respond to subsequently submitted comments for what has now been over three years.

AATB has in the past also supported the concept of tissue-specific legislation that would clarify and appropriately tailor FDA's authority to regulate human tissue. AATB developed its legislative prospectus in order to specify the issues it believes any proposed tissue legislation should include.

AATB commends FDA for the plan that we are here today to discuss. AATB believes that FDA had done a conscientious job in including the tissue banking community from the earliest stages of this effort, and in listening to our concerns, and finally, to rapidly producing a comprehensive blueprint for rationalizing the regulatory universe for cellular and tissue-based products.

AATB recognizes that the current plan embraces a host of technologies in addition to conventional tissue technologies which may be newer and more complex than conventional tissue and which may present FDA with unique regulatory challenges.

The tissues recovered, processed, stored, and distributed by AATB's members fall predominantly within the category that FDA's plan terms conventional tissues.

My remarks today are therefore focused on FDA's plan as it could apply to convention tissues and affect the organizations that recover, process, store, and distribute them.

AATB supports FDA's stated intention to rely primarily on the provisions of the interim rule as finalized to regulate conventional human tissues. AATB submitted extensive comments on the interim rule and believes that its provisions constitute a sound foundation for the regulation of those tissues.

AATB looks forward to seeing a final version of the interim rule in the near future.

AATB wholeheartedly supports FDA's plan to require establishments that recover, process, store, and distribute tissue to register with FDA and to list their products. AATB agrees with FDA that it must know who is

doing what in order to adequately ensure the safety of the tissue supply.

AATB also believes that the contemplated electronic filing system could promote easier and more effective communication between the FDA and the tissue banking community.

Because the need for and benefit of such a requirement should be evident to all, AATB would encourage FDA to publish their proposed rule requiring registration and listing as soon as possible.

AATB also supports FDA's plan to require that the labeling of, and promotional claims for, tissue be clear, accurate, balanced, and non-misleading. AATB believes that the tissue labels should state the type of tissue, the method of processing used to remove impurities or render it disease-free, the methods of storage and handling recommended to prepare the tissue for transplantation, the expiration date, if any, by which the tissue should be used, and the name, address, and phone number or fax number of the distributor.

However, AATB believes that tissue labels and labeling should not be required to bear specific indications for use.

AATB supports FDA's plan to require the screening and testing of all allogeneic tissues for

transmissible disease. AATB does not object to FDA's plan to mandate testing and screening of reproductive tissue intended for use by the intimate partner of the tissue donor.

AATB also supports the plan's contemplated recordkeeping requirements for tissue establishments. We believe that tissue establishments should be prepared to maintain records adequate to permit each tissue to be traced from the donor to the health care provider to whom it is delivered.

AATB believes that the contemplated screening, testing, labeling, and recordkeeping requirements should form the core of FDA's contemplated good tissue practices. Any additional GTPs contemplated by FDA should be narrowly focused on preventing disease transmission and ensuring tissue integrity.

We are concerned about the scope of FDA's contemplated adverse experience reporting requirement for tissue establishments. As I am sure you are all well aware, a tissue establishment may receive many reports of surgical complications or poor surgical outcomes wholly unrelated to tissue used for the procedure.

For these reasons, AATB would urge that the criteria for reporting adverse experiences be carefully considered and narrowly defined. Moreover, tissue

establishments possess no mechanisms to require entities who receive the tissue to inform them of any untoward outcomes. AATB would therefore urge FDA to limit a tissue establishment's obligation to reporting only those adverse experiences to which it is informed.

AATB believes that the requirements of the interim rule, coupled with the requirements addressing registration, listing, and the core of good tissue practices discussed above should constitute all of the necessary regulations for the establishment that currently recover, process, store, and distribute conventional human tissues.

However, some of AATB's members either now or in the future may handle tissues that fall within the definition of more than minimally manipulated and may distribute tissues intended for non-homologous use.

For this reason, I would like to comment on these two categories of tissues. First, AATB believes that tissue facilities that distribute tissues that physicians may use in a variety of surgical procedures should not be charged with determining whether such use is homologous or non-homologous, and should not be required to make a pre-market submission to FDA based on the potential use of the tissue.

A tissue facility has no means to monitor a surgeon's use of a tissue once it is distributed. In implementing the criteria of non-homologous use and more than minimally manipulated, it should be obvious that the devil will be in the details. Although FDA has provided a glossary accompanying its plan, the definitions provided constitute vague and plastic criteria which are certain to cause anxiety and confusion among many of AATB's members.

The flexibility of these criteria also may lead to future disagreements with FDA over the appropriate regulatory category for a particular tissue. For example, FDA's plan defines more than minimally manipulated tissues as tissues combined with non-tissue components.

While AATB believes that it may be appropriate to require pre-market submission for innovative tissue-based products that combine tissues with drugs, devices, or biologics, AATB is concerned that the phrase "non-tissue components" could sweep too broadly in encompass tissue processing aids routinely used in the processing of conventional tissues.

Finally, AATB believes that FDA's plan must incorporate a mechanism for inter-center coordination beyond the role assigned to the recently organized Tissue

Reference Group. Vigorous administrative coordination is required to ensure the products assigned to different centers are reviewed not only according to consistent regulatory policy, but also within comparable time frames.

AATB again commends FDA for its remarkable effort thus far and looks forward to continued communication with FDA as the various elements of the plan are incorporated into proposed rules and published for public comment.

Thank you.

DR. EPSTEIN: Thank you. Do we have any questions or comments from the panel?

MS. PENDERGAST: I have a question about the proposed time frames, comparable time frames between the two centers. I take it you are referring only to when there is an application.

DR. MAY: Well, perhaps, but as other speakers have indicated, there is a certain vagueness in the current description of how exactly the group will function. You have heard that a lot, and that is a concern to all of us.

I think that my comment is basically based on history in which sometimes you can have a rather extended process in getting an answer about a particular tissue

that you have a question about, but I think to be official, we would have to say, yes, that would probably be an official application.

MS. PENDERGAST: I hear you about having SOP, so if you asked a question of the Tissue Reference Group, they can give you an answer within sort of an understandable time frame, but with respect to applications, let's say some applications are going to biologics and some to devices, what time frames do you think they ought to be reviewed under, do you have a model in mind?

DR. MAY: I could put together a proposal for you and submit it with written documents. I can answer for myself off the top of my head, but I would rather, since I am representing AATB, ask the membership or do some survey that says what would be appropriate.

MS. PENDERGAST: Thanks. I mean other than as soon as possible like yesterday.

DR. MAY: Yes, that's quite right, yes, yesterday.

DR. EPSTEIN: Amanda.

MS. NORTON: I would like to say I appreciate your comment that the Tissue Reference Group isn't here today saying this is how we are going to operate, and part of that is because we want to hear from you as much

as possible about what your needs are before we make those determinations, but I think it is important to remember that 21 CFR Part 3 is in effect today and is available to anyone who wants to ask a question about jurisdiction of a product, and that is a 60-day process.

The way it works for those of you who aren't familiar, as part of the request that you make to my office, is that you make a recommendation as to how you believe what you are asking about should be regulated, and if we do not respond within 60 days, that is the answer. Your recommendation becomes the operative decision.

So, it is a very real 60 days, and, you know, it is one that I think we have had a good track record, we believe the process is working pretty well, but obviously, if it isn't, we want to hear about it, because this is a process very much designed to be responsive to people who are regulated by FDA, not just tissues, but anybody.

So that process is in place. What we are trying to do with the Tissue Reference Group is to see whether we need to -- and I think we do -- need to have a highly specialized group that will be able to field and respond in a variety of ways to your questions, but not in any way to provide a two-tiered system or multiple sites for

answers. The coordination factor and the timing factor are very much of considerable concern to us.

We have a system in place. The question is what sorts of modifications and additions might be useful for this particular area where we recognize that there are a lot of things out there that we really may not know about yet.

That is why we really welcome, let me say one more time, and I won't say it again, we welcome examples, questions, things that focus on where the margins are, the what ifs, in whatever way you can present them to us for us to deal with.

DR. EPSTEIN: Randy, can I ask you a question? You commented about the labeling provisions and remarked that the tissue provider ought not to be held accountable for all the inventive things the surgeon might do.

I think that we can all understand that point and that we have been careful in the document to try to stay away from the issue of surgical practice. On the other hand, I think it is easy to envision that tissues may in fact be processed for highly specified functions that might not be generic, as it were, or homologous.

One example might be a bone screw. Bones are not normally screws. I guess the point that I would try to clarify is do you not agree that there is a line

somewhere to be drawn where there is, in fact, promotion for non-homologous use and where these kind of label provisions ought to apply to the provider on account of what the tissue is "for," the intended use.

DR. MAY: I am sympathetic to what you have said, but I would like to agree with the previous responder up here who said that there is really a continuum here, and so that if I have a bone strut that happens to be shaped the right length, so that a previously approved device, a fixation screw can be used with it, to affix it, then, that is bank tissue. As you are saying, if it is bone shaped as a screw, then, it has two functions. It has bone as bone because it will heal into the bone, but it also has this screw function that is built into it, which is a different function.

So I am sympathetic that that is looking a lot more like a device without prejudging that. But, really, you know, there is a continuum along that and where I guess all of us are having concerns and perhaps you, too, is that in the middle of that continuum is where the nice process tends to break down.

So, for instance, if I could just use as an example, a previous one, and that is whether demineralized bone powder should be a Class I device exempt or whether it should be basic bone.

I think there are two concerns about that, that illustrate this problem we are discussing, one of which is a product like that, that is graft on, was issued a piece of paper that says this is bank tissue, and yet in this proposal, it is a device Class I exempt, and in the proposal that you are making, you have been saying, gee, the more we use tissue and the more we roll it out and the more we know about it, there might even be declassifications of it as we get to be more familiar with that type of use, and that this will be an ongoing and dynamic process, yet, this is an example going in the other direction.

Of course, it may not have been an absolutely official position that, say, Grafton was -- and the people that make Grafton probably will want to talk more about this -- but doesn't this go backwards a step instead of towards more declassification with ever-more knowledge about that material.

The other thing about demineralized bone is if we view tissue as a raw material that we take away things from, and the reason we take away things from it, is to have it be the remainder of the device that the physician needs to use, let me just run down, if I have time -- you can tell me about that -- let me just run down if I want to use a patellar tendon, then, processing will include

getting rid of all the muscle, but leaving the tendon, so that that could be considered minimal processing.

Then, to move one step further down, if I want to use a femur, another bone as femur, then, I may want to get rid of all the muscle and all the tendon, okay, or for a femur head or something like that, so then I have a two-step processing, and then that is still minimal processing.

Then, if I take that bone and say, yes, but I want to fill a void space with this, I have two choices. I can either custom-cut that bone to exactly fit that void space, and plop it in there, or I can grind it up and demineralize it and put it in the void space, and that will be essentially turned into the bone that will fill that space, and that grinding it up, I am making it a more convenient use and helping the surgeon to have a material that will behave like bone in there. It will do the things that that ground bone would do.

But these are three levels of processing and as you go down that and are viewing it in terms of mineral processing, the first two steps are things we all agree, okay, that is normal processing, and now when we get to the demineralizing processes that is removing the calcium that will then allow the bone to fit in here and make new

bone, then, all of a sudden that is one bridge too far, and then that is too much processing.

So, I would represent to you -- and it has been said before -- that taking things away from the native material in order to give the surgeon that which he needs and only that which he needs, without germs and without hematopoietic tissue and without other things attached to it, may be an interesting paradigm, an interesting way of looking at it and might help in decisions and clarifications of what is mineral processing.

But as you can see, mineral processing because it is a continuum, is a slippery slope sort of.

DR. EPSTEIN: Thank you. Other comments?

DR. PEREIRA: When we say Class I exempt, as I hear you, you are saying that it is like a higher level of regulation that gives your pause.

DR. MAY: Is it a device?

DR. PEREIRA: What about Class I exempt is a higher level of regulation than what would be imposed on a comparable tissue?

DR. MAY: I don't know, and perhaps therein lies the devil in the details, but if it is a device, that is different from a tissue. That's my point. So I can take the muscle off, I can take the tendon off, I get down to where I took the calcium out, so I can put it inside, and

all of a sudden this is a device even though I have only taken stuff away from the native material.

DR. FLAMM: Demineralized bone is an area that we spent a lot of time discussing because on the one hand, we were all comfortable that this was not something that required greater regulation, and the issue for us was is it that we have experience with it and therefore we know that removing the calcium from the bone doesn't disturb the function in these uses, and therefore it is okay, or is it a priori that one could think before having experience with it, that removing calcium from bone doesn't affect the bone.

We decided that, for example, grinding does not affect and therefore, in your example of grinding up the bone to fit it into the space, we call that minimum manipulation. But our problem was we couldn't see how one could say that calcium is not an intrinsic component of bone, such that if you didn't have great experience with it, you would be able a priori to say yes, removing calcium from bone does not in any way affect the intrinsic biological structural characteristics of bone, such that we can say this is minimum manipulation and that if somebody else were to do something similar in an area where we don't have experience, we also would say this is minimum manipulation.

I mean the problem for us is we are trying to define general criteria that are going to work down the road in cases where we don't have experience, and what we have essentially said is when we get experience with a process that we are comfortable does not affect the biological characteristics, the relevant biological characteristics of that product, then, we can say, well, we may have thought it did before, such as cell separation, now we see it doesn't, and so it is still minimum manipulation.

On the other hand, if we have experience and it does alter the basic biological characteristics, but not in a way that affects the function, then, we can develop standards or develop a process by which we allow this to be minimally regulated without affecting our general criteria by which we classify something as minimally manipulated.

So, your view, and I guess I would ask the American Red Cross also, that you would be comfortable saying that removing calcium from bone as a principle is minimal manipulation, such that, in general, any other tissue where you would remove something as intrinsically a part of that tissue, you would also say as long as you are removing its minimum manipulation as long as you are not adding, it is just minimum manipulation?

DR. MAY: Yes, I actually would say that, and that sort of addresses the homologous/non-homologous issue, too, which also becomes bound up in here, because many tissues, whether something is used in an exactly homologous situation is a question, and many tissues are effectively used as tissues, but in a slightly different location.

Some of the most difficult matters that we are dealing with here are these two points, and instead of just having an arbitrary thing in which someone has to decide how many steps of processing is beyond minimal, or what chemical composition of processing is beyond minimal, I think that personally I would like a paradigm that says as long as you are taking material away from a naturally acquired tissue, and not putting into it, and not augmenting its function in any way, but you are preparing it for the surgeon so he may use it to get the relevant healing process, then, that should be what used to be called bank tissue, and it's now I guess it's called tissue, because that doesn't create any great difficulty with regard to add-on materials which gets you over into the biotech realm, but it also helps with consistency, because if I take some cortical bone and mill it into a strut, and put it in a back, is that homologous?

Yet, through practice that is one of the major uses of bone and a good one. So, you are constantly having to fight the thing that I have seen today, which is saying, on the one hand, there is a lot of data that this works, and on the other hand, we are very comfortable that it doesn't transmit disease, and yet we have to worry about, well, how much processing is over the line.

As long as the process is subtracting something away from it, and that is why I used that three-step model and showed you that actually how much material you are taking away from the natural product really is dependent upon the surgeon, what he is using the material for.

That is why I said you probably wouldn't object if I cut this bone in a triangle to fit in a triangle void. That would be minimal processing if I milled it into a triangle. But if I say this is a very irregular space, and I don't have a computer and cutting edge that will actually cut this bone to the exact defect in the patient's bone I have to fit yet, and the technological development of tissue, then, the traditional role for this has been to grind up the bone and demineralize it, and fill the vacuum and let the body finish it off for you by putting the calcium back in.

You know, I am not really sure that that then constitutes a device per se. It is using the natural mechanisms that the body normally uses. I don't want to belabor that point.

DR. EPSTEIN: Thank you. We appreciate hearing that point.

Marty, briefly.

MS. WELLS: Does the AATB have a position yet on the use of accrediting bodies for compliance with the regulations?

DR. MAY: Yes.

DR. EPSTEIN: Jeanne, would you like to be recognized at the microphone?

MS. MOWE: Yes. We have a prospectus in which we said that we felt --

DR. EPSTEIN: Kindly identify yourself for the record.

MS. MOWE: Pardon me. Jeanne Mowe, American Association of Tissue Banks. Yes, we do have an official position in which we think that we would be delighted to exercise the option to do inspection on behalf of the association.

DR. EPSTEIN: Thank you.

I think we will move on. Do we have a speaker for the American Academy of Ophthalmology? I was told that that request was withdrawn.

[No response.]

DR. EPSTEIN: Okay. Our next public presenter is Richard Russo.

MR. RUSSO: Good morning. My name is Richard Russo and I am speaking today as the chief regulatory officer for Osteotech.

For the record, Osteotech does process demineralized bone. Osteotech develops, processes, and promotes the use of allogeneic non-viable structural and soft tissue grafts for use in musculoskeletal reconstructive procedures. We wish to thank the FDA today for the opportunity to comment on the proposed framework for the regulation of cellular and tissue-based products.

The bedrock of regulation in the protection of public health for non-viable allogeneic tissues is the prevention of the transmission of infectious disease via the unwitting use of contaminated tissue. The central method of preventing such transmission is the consistent controlled and adequate screening of tissue donors via medical histories, lifestyle analysis, and serologic

testing, such as is currently mandated by the interim rule for the human tissue intended for transplantation.

This donor screening is strategically important because most tissue is processed without a means to inactivate or remove viruses should contaminated tissue be donated and the contamination not detected through screening.

As FDA considers the adequacy and appropriateness of the proposed regulatory approach, as well as future regulatory requirements, we suggest that the FDA remain aware of the organizational structure and trends in the tissue banking industry.

The tissue industry is characterized by the networking of many groups carrying out the various aspects of the functions of tissue recovery, the gathering and assembly of relevant donor medical history and personal data, serum handling and testing.

At the same time there is a trend in the industry towards specialization and centralization of certain key functions, such as tissue processing. The language of the current interim rule, when interpreted from the perspectives routinely associated with FDA regulations, is ambiguous about which functional groups within this network of organizations are responsible for which functions.

The question arises, should the regulations be clarified to specifically assign responsibility on a standardized basis to various groups within this network or should the firms operating in this environment be charged with developing a documented and qualified system appropriate for each situation.

MS. PENDERGAST: A question and a comment on your point about treatment INDs. Just so you know, the FDA has presented to HCFA our view that things that are under treatment IND ought to be paid for by HCFA on the ground that it meets their statutory definition of therapy that is reasonable and necessary. So we are working on HCFA on that, and would be willing to have particularized discussions between a company that has a treatment IND.

MR. RUSSO: It was implied in the February 28th documents, but I wanted to amplify that.

On December 19, FDA's Human Tissue Program staff met informally with representatives of AATB, EBAA, and the ASRM to discuss concepts and proposals that might be included in future proposed regulations defining good tissue practices.

During that discussion, certain proposals and situations were raised that I wish to note and comment upon. There was a proposal that tissue firms report any

tissue testing or processing errors for tissue that had been released to use and that might result in the transmission of disease to the recipient, in addition to the reporting of accidents and investigators or complaints on a more periodic basis.

We commented at that time that the proposal for the reporting of errors is inappropriate or unnecessary because this particular requirement does not appear to serve a useful function in the case of tissue-based and cellular products. We note that this proposed requirement was not mentioned or included in the documents released on February 28th, and we suggest that it not be included in the proposed regulations designed to implement the FDA's regulatory approach to these products.

Also, the proposed GTP requirements, as presented at that time, did not include any mechanism for requesting a variance or waiver from specific GTP regulatory requirements in the event that such a variance could be justified through process validation or equivalent means. Such a mechanism including a designation of the group within the FDA charged with the responsibility for receiving, evaluating, and either approving or denying such requests should be included in the proposed GTP regulation.

A reasonable standard for timeliness on the part of FDA in responding to such requests should also be included in the proposed regulation.

Under this proposed regulatory approach, it appears that the routine regulatory submissions would not exist for many structural non-viable allogeneic tissue products. Therefore, the typical means that might be used for other product categories to communicate and justify such requests, such as the submitting of a PMA supplement or a 510(k) will not be available to certain groups of tissue processors. Without such a mechanism, it would be left to field inspectors during on-site inspections to determine the acceptability of such a variance, a situation that we believe would probably be problematic.

Finally, the proposed GTP regulation that was reviewed in December included requirements for process validations. Although these was no specific mention of a requirement for prospective validations, we note that such requirements are becoming the norm for other categories of medical products regulated by the FDA.

We point out that sufficient supplies of tissue appropriate for use in prospective tissue validations are not routinely available. Therefore, we suggest that FDA formulate a position concerning the adequacy of

retrospective validation data or the use of surrogate materials and process validation studies wherever possible for cellular and tissue-based products, and then communicate this position to both the industry and the field inspectors.

The proposed regulatory framework seems to require the gathering and submission of clinical data to assure the safety and effectiveness of non-viable allogeneic structural tissues that are more than minimally processed other than demineralized bone matrix.

No recognition is given to the possibility that laboratory in-vivo or in-vitro data might be able to address the issues that are the source of concern at least for this class of tissues. We believe that such data might be adequate in at least some circumstances and we urge FDA to allow for this possibility in the proposed regulations.

Also, we note that CDRH had used a flexible approach to the generation of clinical data for pre-market applications, such as the use of human performance data generated by healthy volunteers and the approval of a stair-climbing wheelchair.

This data fulfilled the need for clinical data and we suggest that FDA apply similar flexibility to the non-viable structural allogeneic tissues that might

require clinical data whenever such an approach can be justified.

I was originally planning to make mention of the concepts of minimal manipulation and homologous use, but I am going to hold those comments for our docket submission because I am not sure that I understand those concepts well enough for it to be useful.

So I would like to address the issue of demineralized bone matrix as such seems to have generated so much attention. One form of non-viable allogeneic structural bone tissue that has become significant for large numbers of clinicians, both surgeons and dentists and their patients, is demineralized bone matrix.

As you can see from the comments, it has also become an important product for this industry in general and also for Osteotech. FDA's distinction between demineralized bone matrix and other forms of non-viable allogeneic structural grafts used for the same purposes merits comment and raises some questions.

It has been almost 32 years since Dr. Marshal Juris published his seminal work in this field, bone formation by autoinduction in the Journal of Science. In this article, Dr. Juris reported the discovery of the mechanism of autoinduction, currently referred to as osteoinduction, and the fact that appropriately

demineralized bone matrix triggers this natural pathway or mechanism of bone formation.

Since that time, hundreds, if not thousands, of articles and presentations concerning this subject have given or published. Although primarily a subject of interest to bone scientists until the last decade, both the scientists and this type of graft have become clinically important as reconstructive surgery has become much more common, and as surgeons have become more aware of the aware of the biological factors influencing the bone formation and the results that they are trying to achieve in surgery.

The science in this area has improved. It has moved over time from university laboratories to more controlled research settings, and improvements in graft characteristics and processing methodologies have appeared.

It should be noted that the purpose of demineralization is to enmass osteoinductive characteristics inherent in the bone as a complement to the osteoconductive features. Demineralization is not a preservation step for non-viable allogeneic bone tissue, nor is it performed primarily to disinfect the tissue.

We are unsure of the actual number of grafts in use in the United States on an annual basis, but we are

confident that the number of bone grafting procedures in which demineralized bone matrix is used is growing sharply.

Osteotech alone has processed, and clinicians have used, over 455,000 graft-on and demineralized bone grafts in the last several years, so we believe that there is a clinical history here.

Although it is not clearly addressed in the documents outlining FDA's proposed framework for the regulation of tissue-based products, it is our understanding that FDA considers demineralization to be greater than minimal manipulation of tissue because the purpose and result of demineralization is to enmass the osteoinductive features of the bone tissue.

We note that the document outlining FDA's proposed regulatory framework refers several times to the fact that demineralized bone matrix is more than minimally manipulated, but the text never refers to the results or effect of demineralization is to render the resulting tissue osteoconductive and osteoinductive.

The document notes that FDA expects to propose to an orthopedic and dental advisory panel that demineralized bone matrix be classified as a Class I 510(k) exempt device that is also exempt from Part A20 GMP controls.

We suggest that FDA reconsider its intent to treat demineralized bone matrix as a pre-amendment device and its intent to proceed with the time-consuming and somewhat uncertain regulatory processes involved in device classification.

Instead, we suggest that FDA take into account its own regulatory approach that it is proposing now and consider the 30-plus years of experience in what must be now approaching over a million grafts in terms of clinical experience as a basis for determining that demineralization can now be considered minimal manipulation as provided for in the February 28th document.

We wish to emphasize at this time that the facts concerning the osteoinductive characteristics and other features of demineralized bone have been described widely in clinical and scientific literature for many years. The use of this form of tissue has been promoted for appropriate use based upon these particular characteristics, and, in fact, this form of tissue processing was developed over 30 years ago specifically to obtain these characteristics.

We believe that it is of particular importance that FDA should explicitly signal its intent to not interrupt the process of medical and service education

and promotion surrounding the osteoconductive and osteoinductive characteristics of this form of tissue.

We note that should FDA wish to establish particular controls concerning the processing or labeling for this form of tissue, it can do so while treating demineralized bone matrix as minimally manipulated human tissue.

DR. EPSTEIN: Mr. Russo, I need to ask you to try to conclude.

MR. RUSSO: I will be done in a minute, sir, yes.

It can do this via the development of good tissue practices relevant in particular to demineralized bone matrix that would function as the equivalent of special controls. It is our understanding that such an approach has been proposed in some way for the regulation of allograft heart valves.

I can withhold the rest of my comments if we are running late and submit them via the docket, if that is what you wish. I have another two or three minutes.

DR. EPSTEIN: We probably will have a little discussion time available after we conclude this section, and you or anyone else who was interrupted can come back I think at that time.

Do we have questions from the panel?

DR. SIEGEL: Would you clarify your proposal regarding retrospective validation or surrogate material validation? I would like to understand better what you are suggesting.

MR. RUSSO: Surely. Sometimes when you are looking at the validation of tissue, obviously, you would like to use actual tissue in the validation process, but since most tissue is in sufficiently short supply that using it as material for a process validation step is not readily available, and also it is typically donated for a specific purpose, such as either clinical and/or clinical and research uses. So let's just say it flies in the face of the purpose of donation that is explicit on an informed consent document to use it for machine validation, let's say.

DR. EPSTEIN: Could I get you also to comment on your remark that you didn't think that there was a purpose in reporting of processing errors that might be linked to risk of infectious disease, and I didn't quite understand the thrust of that argument.

MR. RUSSO: I was probably trying to comment on too many things too quickly.

It is our understanding that the reason why in such things as blood products or blood derivatives that error reporting is important is because of the large-

scale pooling of tissue and the number of people who might be receiving tissue from any one donor.

Those facts we don't believe are germane to this particular issue. We do believe that keeping the records of all those complaints and everything would be appropriate, but to report them on an incident basis wouldn't seem to really serve anything unless you were going to ask for some notification of doctors or something like this.

We were unclear as to what the purpose of that was.

DR. EPSTEIN: I think that we had in mind that such data be retained in records and that it be available on inspection. I don't think that we were contemplating a filing requirement. For the record, blood components are a single-donor product, so the issue of pooling is not entirely a distinguishing feature.

MR. RUSSO: We were thinking of things like factor VIII and things like that.

DR. EPSTEIN: Ruth.

DR. SOLOMON: Just to clarify, at one time we had presented a proposal to have errors and accidents related to communicable disease transmission reported, but we have rethought that.

I wanted to ask you something on what you meant by having a variance. Do you have in mind what we currently have in the regs for blood products, which is 640.120, an alternative procedure whereby you would show that what you are doing is as good, if not better, than what we would like you to do, or did you mean a complete exemption saying I don't have to do this?

MR. RUSSO: I meant a variance such that it could be demonstrated through process validation that the requirement could be met some other way, as good as if not better.

MS. PENDERGAST: Do you see value in error and accidents from the point of view of the company? I mean does it tell you what you are doing well and what you are not doing well?

MR. RUSSO: From a quality assurance standpoint, clearly, trending of all sorts of errors or let's just say defects or deviations from your process is useful, and that should be on file. I think for most firms involved in tissue processing on a large-scale basis, that is probably already being done.

I was referring to originally what Ruth was saying, in the December 19 meeting, was presented more of as an incident-by-incident approach, and it was informal meeting, so we didn't have notes from it. But I wouldn't

see a problem with complaints and similar things being summarized, so that an inspector could review them or something to that effect.

DR. EPSTEIN: Kathy.

DR. ZOON: I would see them important in any quality assurance program because in order to assess the quality of your operations, you are going to have to see where the problems are internally themselves.

MR. RUSSO: And that the trends are in the right direction.

DR. ZOON: That is correct.

MR. RUSSO: Right.

DR. EPSTEIN: I think that there is also a public health dimension if these data are not retrieved and made available, then, they can also never be summated.

MR. RUSSO: You are correct. I guess to make sure that I am not misspeaking myself, I am not saying that the data shouldn't be accumulated by the company and not be available. I was merely referring to the proposal that was bandied about in December about an incident-by-incident report, that I didn't think presented the agency with any information unless you were going to take some actions that we didn't understand.

DR. EPSTEIN: Other comments from the panel? Questions?

Thank you, Mr. Russo.

DR. EPSTEIN: We have come to the point in this section where all those who had previously requested time at today's meeting have had a chance to present, and will do two things now. We will recognize additional public participation and if there are questions for the panel, I would request that they be brought forward on the cards that were distributed .

Do we have any additional requests to present? Dr. Strobos.

DR. STROBOS: Could I ask a question or do I have to use the card?

DR. EPSTEIN: You don't have to use the card right now.

DR. STROBOS: I am Dr. Strobos. I am with Biocoll. I had a question about this DFDBA plan or the demineralized bone plan.

You seem to be suggesting that the level of regulation for a Class I exempt 510(k) exempt GMPs would be identical to the regulation under the bank human tissue program, and I guess one specific example we have just identified that is different has to do with reporting requirements.

I presume that Class I exempt products would not be exempt from the device reporting requirements, or would that be another exemption that would be provided under the Class I designation?

DR. EPSTEIN: I need to turn to one of our device experts.

DR. RICHTER: My understanding is that we would also exempt from the reporting requirements.

DR. STROBOS: Then, I guess the next question is there are these provisions relating to 510(k) modifications. I mean you can sort of go down the path, but there is a 510(k) modification path where as you go through that path, there are certain modifications that you would have to file.

And then the question becomes do you -- let's say, for instance, you take demineralized bone and add an inert compound like glycerol to it. Would that addition to that Class I exempt device make it still a Class I exempt device or does that make changes, and then how far do we go along in that in terms of 510(k) modification?

DR. RICHTER: I think that is one of the things we have a Tissue Regulation Group in place to address on a case-by-case basis with input from both of the centers, and it would depend on what the material was that was being added, but you are right, if the product remains a

device, depending on its intended use, and so forth, ultimately, you know, if it is no longer a Class I exempt, it would be regulated as a device, but depending on what the tissue component would be and what the Tissue Regulation Group would determine, I think it would be handled on a case-by-case basis.

DR. STROBOS: My only point is that there are a lot of differences, I mean labeling, you know, issues with regard to, for instance, whether it is prescription use, non-prescription use. I mean there is a whole array of device regulations that might come into play if it was a Class I exempt that would be different.

DR. EPSTEIN: Marty, have we received any questions in writing?

MS. WELLS: Not for this session, no.

DR. EPSTEIN: Is there anyone else who wishes to make a presentation? Please identify yourself at the mike.

MR. SCHWEIKERT: Hi. My name is Al Schweikert. I am director of Product Development for Theracel. We make cell-based products for neurological diseases, such as Parkinson's and Huntington's, and even spinal cord repair.

Some of our products would be considered minimally manipulated. I will use the slang term in industry of M&Ms because it is easier.

Some of the M&Ms and the regulations associated with them and some of the manipulated cell products, there is actually a caveat there, and that if we do a neurological surgery, the transplantation itself can be in two ways. It can be in a solid graft or it can be in a suspension graft.

The suspension graft is actually manipulated. It is treated with an enzyme solution, so that the cells are disrupted from the tissue. This could be considered a better graft because you are able to measure viability, you are able to do better viral testing, you are able to put the cells into solutions containing antibiotics, so that in itself, although it is maybe manipulated, it is possibly better for the transplantation.

I would just request that the agency stick with its own definition on manipulated and minimally manipulated, and look at cells based on function, not so much as how much processing is done to them.

Thank you.

DR. EPSTEIN: Any comments from the panel?

DR. SIEGEL: I think we will discuss that more this afternoon, but, indeed, as you note in our

definition, I think simply separating cells into a suspension, if their function is not otherwise changed, would probably not per se count as more than minimal manipulation. One would have to look at individual cases in terms of what the potential impacts of the processing are, but I think our intent is consistent with your recommendation.

DR. EPSTEIN: I think we have heard several times that there may be extensive processing that results in what is still a homologous use, and I think that is the point that is concerning people.

FDA's view in approaching this problem was that we did not know a priori if something was extensively manipulated, what would be the case as far as its function, its integrity. So even though the use might remain homologous, a question was raised about safety or effectiveness based on processing, degree of processing, so I think it would be helpful not to blur those distinctions.

There are a set of distinctions related to homologous versus non-homologous use. There are a set of distinctions related to extent of processing.

Yes.

DR. MAY: I am Randy May. Because of the discussion that I heard there about error and accident

reports, I just wanted to make the point that AATB standards require the maintenance of an error and accident log, which is open to our inspectors, so accredited banks have that rule. I wasn't sure from what you all were saying that you all realized that.

MS. PENDERGAST: Randy, could I ask you a question?

DR. MAY: Yes.

MS. PENDERGAST: When your members have an error or an accident, and they write it down, we had an error or accident, what kind of an assessment, self-assessment and change to their practices or whatever are they required to make, if any, and what writing down of what they did to fix the problem are they required to do under your guidelines or standards?

DR. MAY: Jeanne, should I have somebody else address that? I will have our inspector address that.

MR. TAYO: Emmanuel Tayo, AATB inspector.

While the standards don't specifically address precisely how trend analysis is conducted with regards to errors and accidents, with every inspection, it is expected that errors and accidents are recorded, that there is an individual file index that summarizes exactly what the different cases are, that errors and accidents are divided up into different categories, whether they

are related to quality assurance issues, specifically to procedures conducted by personnel in-house, whether they are related to complaints and allegations that have to be investigated from outside, and whether they are just related to routine accidents, for instance, that might involve safety to employees.

I always look for an index, and if there isn't, that is one of the recommendations that is given to tissue banks, and generally, there seems to be widescale compliance with that.

MS. PENDERGAST: Does it then go to say what they did about it? Let's say the employees are making the same mistake over and over again. Does it then list like what kind of training the company did? What is the follow-up?

MR. TAYO: Obviously there is a range, but in many of the best establishments they really have got very good documentation where they actually document, for instance, actions that are taken to resolve an issue.

They actually for each incident make sure that the case is resolved and document what was done to resolve it, and in many cases, as a result of these things, there are changes made to standard operating procedures and other sequelae.

MS. PENDERGAST: Thank you.

DR. EPSTEIN: Please.

MS. MOOGK: I am Margery Moogk from the Northwest Tissue Center in Seattle. We are a nonprofit, full-service community tissue bank that is responsible for serving hospitals and patients in Montana, Washington, Northern Idaho.

I would like to echo most of the compliments that you all have received today about this regulatory framework, but I would especially like to thank you for the indication that you are going to return human heart valves back to the fold of human tissue. We really appreciate the opportunities we have had to meet with you and hopefully educate you about the safety record that we have, and again, just thanks for putting us back where we think we belong.

DR. EPSTEIN: Thank you, Margery.

Does anyone else wish to comment?

All right. Let me just thank all this morning's speakers and presenters. We will have our next session commencing at 1 o'clock on autologous and other cellular therapies. Until then, we on a lunch break.

[Whereupon, at 11:58 a.m., the proceedings were recessed, to be resumed at 1:00 p.m.]

AFTERNOON SESSION

[1:05 p.m.]

DR. SIEGEL: I would like to call the group to order again for our afternoon session, which will be on cellular therapies largely other than stem cell therapies which will be discussed later in the afternoon.

I have been asked to announce that speakers, particularly if you have already prepared a prepared text, if you could get a copy to Marty Wells if you have yet to do so. That would be very helpful.

Autologous and Other Cell Therapies

DR. SIEGEL: I am Jay Siegel. I will be moderating this session. Our first speaker is Dr. Philip Noguchi of Office of Therapeutics, Division of Cell and Gene Therapy.

Phil.

FDA Introduction to the Issues

Clinical Safety and Effectiveness

DR. NOGUCHI: I would like to thank you all for being here. Also, a couple of just acknowledgments. I think Mr. Jim Weixel is in the audience. He and I go way back at least 20 years with this whole thing. So it is sort of like, well, sometimes we get things done here, and I am just happy that Jim is here, along with Claudia and everybody else to see this day.

Also, my acknowledgments directly to our most recent commissioner and our current deputy commissioner who really have spearheaded the intense effort that we have gone through in order to finally come to this situation.

I kind of say that is very much like a root canal for those of us who are participating. It is painful, but very necessary to the health of the agency, to the industry, and of course, to the public.

Now, this morning there was obviously some concerns and discussion about some of the terms that we call are the kick-up kinds of considerations, that is, in addition to the basic fundamentals of good recordkeeping, good tissue practices, and infectious disease control, what are the things that might cause FDA to want to see pre-market submissions.

A couple of these I think are relatively straightforward. For example metabolic use in general we would consider things that are being designed from human tissue that cause a metabolic effect to normally require pre-market types of applications although we have said in this document that we think that for hematopoietic stem cells, there may be sufficient evidence out there to not necessarily require that in all cases.

Certainly for reproductive tissue, I think the question of efficacy is not really the issue. This is something that we have said many times, but more formally here.

Secondary of that, I hope we can clarify a little bit. Richard Russo was talking about such things as tissue combined with non-tissue elements of drug or device-like characteristics. We are thinking here more of what we would call traditional combination devices. You may have an extracorporeal device in which cells are placed to add in detoxification of liver failure as an example.

So these are things that we have already seen. We really are not trying to encroach upon practices of how people are procuring or actually making tissue products, but when they are combined together and they must be together to actually effect a therapeutic benefit.

The two areas which are of obvious concern, and we can share with you that we share these concerns, as well, is the question of minimal manipulation versus more than that, and what is a non-homologous use, and I will spend just a couple minutes telling you what at least we are proposing, and this is open for a lot of discussion.

We have taken some pains to say that structural tissues as opposed to other things, such as cells or metabolic use of tissues, that minimal manipulation would include such things as cutting and shaping, although I think you have also heard that shaping, so that it looks and is supposed to act like a screw, is probably not quite what we mean by mere shaping.

A few other of these kind of preparative things where the fundamental characteristics of the tissue are not changed are what we consider to be minimal manipulation for structural tissues.

I think we have heard a lot of discussion today about the pros and cons for demineralized bone of whether demineralized bone in itself is a special case of minimal manipulation or whether it is something that can be generalizable to a whole class. We are not really sure, and that is obviously why we put it out on the table.

I think the discussion has been very helpful in that regard.

For other tissues and cells other than structural, we have said that more than minimal manipulation is something that alters the biological characteristics of that tissue, and the examples that we have used in the past include such things as expansion of cells, addition or growth factors, exogenous growth

factors, transection, such as you might find in gene therapies.

We had also at one point thought that especially for cellular materials, that cell isolation or subtraction of cells from that, the cells or tissue in order to get a more purified population was more than minimal manipulation. We now think based on the results of a lot of data and clinical results, that no longer is, so that for our current document, if you have a cell population and you are subtracting cells from that, or if you have a tissue, you are subtracting cells from that tissue, we do not consider that more than minimal manipulation at this time.

I am just going to end here with this very brief introduction on a couple of other notes. One question that has come up is how does this tissue policy interact with other initiatives that we may have, does it supersede things.

I think a better way to look at it is this really represents for FDA a way to approach the problem of the use of cells and tissues for therapeutic benefit. We consider this gets you into the ball park as to the kinds of disease controls you may need and whether or not you need pre-market approvals in clinical trials.

Once you get to the point where you require pre-market clinical trials, then, I think it is fair to say that all the initiatives and flexibility that currently apply would also apply to this area if they appropriate. The oncology initiative where tumor shrinkage is one surrogate, well-accepted surrogate of clinical benefit, certainly is appropriate if a tissue is being used for that cell or tissue.

The flexibilities in the manipulated autologous cell document would also be applicable, as well as accelerated approvals, and Dr. Siegel certainly can provide more details on the clinical trial designs and endpoints that are needed.

I just would put a word of caution here, that regardless of whether or not through this process you are required to submit a clinical study in a pre-market fashion to the FDA, especially as we talk about industry standards for preparation, it is not just how you prepare it or what the viability and the end result of that product, but it is how does it perform in a patient and how does your process enhance that above that of an established procedure.

One way or another, controlled clinical trials I think will need to be done so that a baseline can be established, and improvements to that can be measured.

With that, I think I will just end there and turn it back to Jay.

DR. SIEGEL: Thank you, Phil. I would just like to take a moment. As Phil indicated, these products will be subject to a number of related regulatory guidances. Indeed, the comments we received in advance regarding a spectrum of issues including new indications and accelerated approval in serious diseases are comments that, in part, are addressed better in related documents.

I quickly wanted to alert the audience, those of you who don't know, last week the agency released guidances for industry regarding providing clinical evidence of effectiveness -- that is the start of the title -- and regarding FDA approval of new cancer treatment uses, that talk about evidentiary requirements for new indications and the initial document for original indications, as well.

Phil and others have referred to the mess, our guidance of last May up there now, and for the next minute or two, for you speed writers, our voice phone numbers at Center for Biologics where you can request those documents, dial-up fax numbers, or you can have them faxed, the World-Wide web page where you can request them, as well. The accelerated approval regulation is in

the Code of Federal Regulations for biologics, is at 21 CFR 601, Subpart E.

As questions or other comments arise, we may discuss those further, but I will leave that to see where interest lies, and while you are writing that down, I will take this opportunity then to introduce our first speaker, Lisa Raines, Genzyme Corporation.

I don't want people to be distracted, and I see a few people still writing, so why don't we wait another 30 seconds or so, so they can listen to what you are saying.

Public Presentations

MS. RAINES: I am Lisa Raines with Genzyme Corporation, and I am here on behalf of Genzyme Tissue Repair, a division of my company.

Genzyme congratulates the Food and Drug Administration on its proposed new approach to regulating cellular and tissue-based products. We believe that the new framework provides a thoughtful, unified approach to the regulation of both traditional and new products.

I would also add is a recognition of the potential patient benefit that new cellular therapy products do offer.

We especially agree with the concept that "providing only the degree of government oversight

necessary to protect the public health" is appropriate. That is a quote from the February 28th document. In this regard, Genzyme would like to point out that the automatic application of CBER's general safety testing requirement to cellular and tissue-based therapies is, in our opinion, inconsistent with this goal.

General safety testing regulation is not addressed in the new policy issue. It is one of those details that the devil might be in, but we do think it is appropriate to address it early in the development of this new policy.

As most of you know, the general safety testing regulation requires that all lots of a biological product be tested for toxicity in two animal models, mice and guinea pigs, for a period of seven days before being released. This is neither appropriate nor practical for many tissue and cell therapy products.

I would like to focus specifically on autologous cell therapies since that is a field in which my company is involved. Autologous cell therapies are, by definition, custom-made. Each patient's cells constitute a separate product lot. So while traditional biological manufacturers are required to perform general safety tests on a few lots each year, autologous cell manufacturers would be required to perform these same

tests on thousands -- perhaps even tens of thousands -- of lots each year.

We estimate that each general safety test costs approximately $700 to $900, plus the sacrifice of four animals, multiplied by thousands of patients per year. Such testing would result in increased costs for autologous cell therapies and the unnecessary sacrifice of thousands of animals all without any of corresponding public health benefit.

In fact, for some somatic cell therapy products, it may be impossible to preserve the product's purity, safety, and potency for the seven-day period during which such testing is performed. In these cases, requiring such testing would actually undermine public health goals.

We note that certain cellular products, such as whole blood and red cells, are explicitly exempted from general safety testing in the regulation. In addition, general safety testing is waived by regulation, a new regulation that was adopted in May 1996, for specified biological products including gene therapy products.

Genzyme believes that it is inconsistent to require general safety testing for autologous cell therapies, when both certain allogeneic cell therapies and even gene therapies are exempt from this requirement.

As the company whose product is the first to be reviewed under the new policy for cellular and tissue-based products, Genzyme believes that it is essential that this problem be addressed immediately. We believe that there are three alternative ways to accomplish this: To revise the general safety testing regulation to specifically exempt autologous cell therapies and perhaps other cell therapies, as well; or alternatively, to add autologous cell therapies to the list of "specified biological products" covered in that regulation; or finally, to revise the general safety regulation to authorize the center director to waive testing whenever it is not necessary to assure the safety, purity, or potency of a biological product.

Thank you for this opportunity to give our comments.

DR. SIEGEL: Thank you.

Questions from the panel? I have a question. Your comments were focused on general safety testing and for autologous products. Do you see a distinction for allogeneic or is that simply because your corporate concerns are limited to autologous, and you were only addressing those?

MS. RAINES: Well, our corporate concerns are limited to autologous, however, in the case of the

allogeneic products, many of them are mass produced, and that is the reason for using allogeneic, off-the-shelf products, and so we would anticipate that those might be larger product lots and at least would not be as burdensome, so not focusing on the scientific issue, but it certainly would not present the burden of doing thousands or tens of thousands of tests per year for allogeneic products that it would for autologous.

DR. SIEGEL: Thank you.

MS. PENDERGAST: What are the parameters of the exclusion that you want is it just autologous and just when it is patient by patient? What is the decisional rule that would limit like if we were to give an exemption, what do you see the exemption covering and what do you think is outside of the exemption?

MS. RAINES: I think you could very reasonably have an exemption for all cellular and gene therapies, because you already exempt gene therapy, you already exempt whole blood, red cells, plasma, all of those by regulation, and so if you take the least manipulated products, and those are already exempt, and the most manipulated products are already exempt, there does seem to be a certain rationale of exempting everything that is in between.

DR. ZOON: Thank you, Lisa, for your comments. I just want to say that the Center has been engaged in discussions in the regulation rewrite on the general safety test as it is applicable to a broad class of products.

Just one point of clarification. The new regulation for specified biotech products, that is for the vector, so I just wanted to make sure that people didn't think it was for the whole product. At this point, the way it is written, it is for the vector. So, just a slight clarification on that.

MS. RAINES: My reading of that regulation, which I have a copy of, refers to therapeutic recombinant DNA-derived products. That sounds a little broader than just the vector.

DR. ZOON: No, no, no, no. It does apply to the proteins, no question, but with respect to gene therapy, I just wanted to highlight that it is actually the vector that it refers to, not the whole cellular system. Just a minor clarification.

MS. RAINES: Okay. I agree.

DR. ZOON: I just wanted to make sure people -- and we take your point. I think the general safety test is an area that the Center has been targeting and we certainly appreciate your comments and any advice with

respect to autologous and/or allogeneic products other individuals might have.

DR. SIEGEL: I think questions from the floor we are doing at the end of the speakers, if you would please hold that either for orally or in writing.

Thank you very much.

MS. RAINES: Thank you.

DR. SIEGEL: Thomas McKearn, Cytogen Corporation.

DR. McKEARN: I think I used up half my time just getting up here from the back of the room.

My name is Tom McKearn. I was one of the founders of Cytogen back in 1981 and now serve as CEO of the company. I sure hope the company is paying for my trip here today.

First of all, thank you very much for the opportunity to again come and address members of the agency with regard to the evolving status of regulation of this field of cell therapies. For those of you who are wondering why Cytogen would be up here presenting, we are a company located in Princeton, New Jersey, one of the very few biotech companies which have, not one, but two FDA approvals for an oncology product, the last of which was signed, among others, by Dr. Siegel last fall, and in the course of business in 1995, acquired a company

called Cellcor located in Boston. Cellcor has performed over 5,000 autologous lymphocyte therapies. Interesting when they look at their safety record relative to what we were hearing this morning about infectious complications, in that 5,000 they have documented less than 10 incidents of bacterial contamination, all of which were caught before the cells were put back in the patients.

So I think on the safety side, they have an enviable record of performance and, in fact, the world's largest base of experience in terms of this kind of therapy.

They have, as a matter of record, now completed accrual in their pivotal trial for renal cell cancer, and hope to be able to have that application under a BLA in front of the agency in the next few months, so the issues that we are discussing today are of very real-time concern to us at Cytogen and Cellcor.

Now, our discussions on the area of this type of regulation of cell therapy, according to my record, Dr. Zoon, date from July 7th, 1995, when we met in your office and talked about the issues at that time. So, I will try and stick with the same categories we had on the agenda for that day, which included the consistency of standards for cell therapy and the interrelationship of the current proposed changes in cell therapy with other

recently announced changes by the agency under various RGGO initiatives.

In the first category, I would like to make one comment and ask two questions. The comment has to do really with, if I may, the taxonomy of any of these schemes for separating complicated fields into different pieces, bone piles, if you will, no pun intended.

I think there is a couple of principles that may be helpful if applied to the standard. One is to try whenever possible to make dichotomous distinctions, left versus right, so that we know without any further definition exactly what is meant, and bright lines are very useful in this regard.

The second is to avoid in making those distinctions the use of terms which are commonplace in the art, and which, in the classification intended, have a different meaning than that which is used in the art.

So my cases in point with regard to the current standards have to do with the distinction between structural and metabolic. The term "metabolic," when used in this setting, is not meant in the sense that the cells that are structural do not undergo metabolic function, nor is it used in the common sense of the term metabolic in medical practice. By your glossary, it is used to mean systemic.

So my point in raising all this is not to drag you through this at any further agony, its agonizing detail, but rather it serves as a point of confusion to those of us who read these documents when we encounter terms that cannot be used in their converse as applied to the other side of the street, and cannot be used in their common use form when read in the context of this document.

Now, the questions I have are in this area just pretty simple. We have understood at least since July of 1995 that the principles that guide the need for regulation in this field are ones in which the regulation would come into being because the agency felt there was a need to regulate this field.

Secondly, the regulations, when promulgated, would represent the best current understanding of the scientific progress in the field that time, and so my question I guess is are those still the ground rules.

DR. SIEGEL: Yes.

DR. McKEARN: Thank you. There are some people in our shop who thought McKearn, you will never be able to ask a question of the folks at the agency and get a clear and precise answer like yes or no.

The next question. In terms of trying to understand the rationale as explained in the document,

and working our way through that, we are following along in understanding your rationale for the treatment of certain of the cellular therapies, autologous therapies, metabolic function, and we come upon the comments -- I think they are on page 18 of the document -- in which you say that you are going to assert premarketing requirements over those products except when the cells or tissues are used in persons from whom they were obtained or in a close blood relative of the donor, in which case as a policy matter the agency would not require a premarket submission.

So, my question is could you please state what the policy is that you are invoking here.

MS. PENDERGAST: By page 18, you mean of the non-English language version?

DR. McKEARN: Yes, and actually it was funny because the fax copy of ours, it skipped a page in our fax machine, so we spent three days trying to run around in our shop, but, yes, it is under Metabolic function (d), the second paragraph, I believe.

DR. SIEGEL: It exists elsewhere also. It is in the footnote on page 9, as well.

DR. McKEARN: Correct. It is referenced a number of times, but in no case is the policy stated. Our circumstances are that we were marching happily

along, agreeing with you with all these parallels between how you were describing the intent to regulate stem cell therapy and where we see autologous lymphocyte therapy and then there was this break, and the break appears to be driven by a policy -- at least it is referenced as such several times -- so I am asking can you please tell us what the policy is.

DR. SIEGEL: Well, the policy is what is described in here. The question you are asking is what is its foundation, is that correct?

DR. McKEARN: Yes, because you just answered yes, you are going to do things for scientifically well-grounded reasons.

DR. SIEGEL: Well, suffice to say this is an area that has undergone a tremendous amount of debate. There are those of us who think that there are well-founded scientific reasons in part pointing to this distinction, that amongst those therapies that are not more than minimally manipulated and that are not combined with devices, but are metabolic, that where their motion of action is metabolic, or perhaps you are correct, that systemic is a better term, that is something we need to look into.

In fact, I must say that what happened with this and many other terms, is that over months are used, and

where we drew the lines evolved, and the terms didn't always evolve -- the way we defined the terms therefore evolved, we didn't always change as opposed to redefine, and I think it is a point well taken and worth looking into, but in any case, back to your question.

This is not the clear, one-word answer. I could just say yes. But back to the question --

DR. McKEARN: One out of two isn't bad.

DR. SIEGEL: There is a significant scientific underpinning. There is a feeling that issues of rejection, graft versus host disease, and compatibility are less for autologous than they are for allogeneic, but the lines are not very sharp there. It is not the black and white lines that you have talked about.

I think that there is also an important feeling that there are reasons involving -- it is hard for me to speak to this point -- but that there are in the case of these non-manufactured tissues, arguments regarding how best to expend agency resources and how intrusive to be in family decisions that also impacted that.

So what you are looking at is some ambiguity as to where the reasons for that line --

DR. McKEARN: I guess what we would try and petition is for a chance to discuss this aspect and understand how a scientific principle, if applied in this

setting, could cause you to come out on one side in the case of stem cells -- which we think, of course, is the right side -- and come out on the other side in the case of lymphocyte therapies given that per this, within a family, but in a fully allogeneic sense, you would not regulate stem cells, but you would regulate lymphocytes.

DR. SIEGEL: There is a misunderstanding that needs to be cleared up here, which is that there is not a distinction here between stem cells and other cells that fall into this category of metabolic, non-manipulated.

For those that are kicked up solely by virtue of being metabolic, if they are autologous or family-related they will not, in fact, be kicked up into premarketing approval whether or not they are stem cells or some other type of cells.

DR. McKEARN: So that just takes me back to could you then state the policy.

DR. SIEGEL: The policy is that if you are more than minimally manipulated, you move into C2 or 3, and if you are combined with the device or drug you move into C2 or 3, and if you are non-homologous use you do, and if you are metabolic you do provided that you are for unrelated allogeneic use, and that is regardless of whether you are a stem cell or not. My apologies if that didn't come through clearly.

DR. McKEARN: So if you are autologous and metabolic, then, the distinction is made on whether you are a stem cell or a lymphocyte?

DR. SIEGEL: No. There is no distinction made on whether you are a stem cell.

DR. NOGUCHI: It is really, in the case that you are speaking of, for expanded lymphocytes. If these were not expanded, and weren't changed or growth factors were not added, I think that is part of it. No one of these factors is necessarily taken in by itself, especially the metabolic area.

DR. SIEGEL: The cells were given as an example, but we would think that family related, non-manipulated, whether the pancreas, pituitary, any other similar cell, that was minimally manipulated and for homologous function, would be similarly treated to marrow stem cells.

MS. PENDERGAST: Going back to the policy issue that undergirds some of this, we tried to be respectful when we could to the desire of a person to use their own body parts as they saw fit, and also not to get into the middle of family decisions, and we likened it in part to the recognition that families make decisions in other contexts, such as organ sharing, when the government

doesn't intervene in a family decision even if, strictly scientifically, you would say that is a stupid idea.

Sometimes the families want to do things the government and the medical profession sometimes back off, and so we were trying to give some recognition to that.

DR. McKEARN: So help me understand, then, the next step in application of that thinking. If that is true within a family, then, why isn't it true within an individual? Why shouldn't you thusly treat all autologous therapy with that same consideration?

MS. PENDERGAST: Because we felt that when it is in its sort of more purer and normal form, as in the non-manipulated setting, it is very different than the industry that then takes over at the point where it is more than minimally manipulated. Then, it loses, you know, sort of that characteristic similar to like organ sharing among siblings or whatever, so that is why. It becomes much more of an industry type function that we regulate, and that is the distinction that we drew.

DR. McKEARN: I would appeal for more discussion on this point. because I am not sure that these distinctions are as meaningful to those of us on the industry side of the table as they seem to be to folks on your side.

I will be very brief with this next one because I don't think there is an answer. That is to the issue of how we can -- those of us who are planning in the next several months to present you with a BLA on a cellular therapy based on pivotal trial results done in cancer -- which piece of which RGGO initiative is currently sufficiently well understood and meant to be applied, so that we can get this process moved forward unidirectionally?

That is almost a rhetorical question, and you an answer yes to that.

DR. SIEGEL: Obviously, those that are published, that are guidances, the effectiveness guidance, the oncology initiative are relevant. You know, in the phase-in period for the current schema that you are holding today, while it is out there for public comment, our approach in my office has been that there are substantial parts of it that can be followed within our currently -- totally consistent with our current regulations, in our current regulatory structure, and to the extent that it doesn't require violating our own regs, and it represents our current thinking as to the best thing to do, it is our intent to follow this.

Now, there is other parts of it that will require some regulations, and yet there are other parts

of it that might not require those regulations, but we would like to clarify through regulation, but we will try to phase in.

DR. McKEARN: Let me try and ask the question in a way that isn't really product-specific. So for those of us who had a pivotal trial that was initiated before the announcement or RGGO, that spelled out certain primary and secondary endpoints, the literal interpretation of the RGGO initiatives in oncology is to elevate what had been secondary endpoints to primary.

Would that be an expected outcome from the discussions we would have with you?

DR. SIEGEL: I think when during the course of the development of a product, the agency develops additional guidance or approaches to how it should be developed, we try to work very flexibly, I think is the operant word, with companies to figure out the fairest, most appropriate way to phase in from earlier advice to later advice, and certainly with the oncology initiative and with much of what we are looking at here, that would be our intent, but obviously, it is the sort of question that deserves an answer on a product-specific basis through discussions, and we would be delighted to discuss them with you and with all others here who have similar questions.

DR. McKEARN: I will take that as a tentative yes.

DR. SIEGEL: A definite yes. But I forgot what the question was.

DR. McKEARN: Are you going to give us our approval?

MS. PENDERGAST: I would just like to expand your question slightly more broadly. Although I think the innovation in our thinking, as Jay indicated, will be applicable to review, the fact of the matter is, though, that whatever rules are in place now, are the rules that are in place now, and they will stay in place until we change them.

So, what that means is, is that as a formal matter, this policy proposal that we are announcing doesn't change the landscape. If you are required now to file a 510(k) or Appeal A, or whatever, you have to do it until you don't have to do it.

DR. McKEARN: So we would probably, then, be best served by requesting a meeting, so we can clarify the ground rules that will be operant as we move forward. Is that what I take away from this?

MS. PENDERGAST: Yes.

DR. McKEARN: Well, that is very helpful, and we appreciate that input.

DR. NOGUCHI: But it is true for all manufacturers of autologous cell products that are under premarket approval requirements can file a BLA. That, we did specify in January.

DR. McKEARN: Thank you very much.

DR. NOGUCHI: So that is a yes.

DR. McKEARN: That is a yes, too? Man, I am leaving with a whole armful of yes's.

DR. NOGUCHI: Yes, for the submission. I didn't say anything about the review.

DR. McKEARN: We will take whatever you will give us.

Thank you very much.

DR. ZOON: I just want to make one comment about that metabolic function, because I think that section has undergone an evolution over time even in internal thinking, and your points are well taken about some of the clarity of presenting that, and we will certainly take that, Tom, back.

I think one of the issues with respect to the metabolic function, and I think we have tried to address in each of the sections, the key factors under which the area of concern was. So if you take the issues of communicable diseases, the issues of manufacturing, processing, and controls, and then the issue of

homologous versus non-homologous, we tried to dissect each of those as a separate category, so you could independently look at those variables, but the reality is you need to look at each section of the document and see where your product falls in with respect to that algorithm, not just one section.

So I just wanted to clarify that because it may be slightly confusing, and I think it is important to point that out.

DR. McKEARN: Okay. Well, we will give it another read.

DR. SIEGEL: I have one last question. Could you help me with the pronunciation of the name of the next speaker?

DR. McKEARN: Fred.

[Laughter.]

DR. SIEGEL: Thanks.

Fred, actually, I am a little embarrassed, but I would have been more embarrassed if I actually tried to say it. Thank you.

Fred Miesowicz from Cellcor and Cytogen.

DR. MIESOWICZ: Well, now you know my name and how to pronounce it. I am vice president and general manager of Cellcor, and assuming this talk goes off good, Tom McKearn will be paying for my expenses today.

I just want to say in the beginning that the FDA's proposed regulation of cell and tissue-based therapies in its unified and very broadly applicable structure demonstrates extremely good progress and understanding about the new and the older therapies that are going to be reviewed by the agency.

What I want to do is make a few comments on several areas of the regulation again to sort of -- I want to say bore in a little deeper from where Tom has gone on some of these definitions, maybe give our own opinion, and then also make some general comments on our own experiences in cell therapy that I would say in a way maybe is a hint for people coming down the line of things they should and maybe things they shouldn't do.

One area we have talked about -- we might as well call it M&M, minimum manipulation, use the abbreviation -- in this area, I think before some of these very good meetings we have had with deputy commissioner Pendergast, we have talked a lot about this.

The way I kind of look at it -- and this isn't in my speech -- but after hearing everyone this morning, I look a manipulation really as how well controlled is the process, how well characterized is the product, how well validated are the steps.

I think to us that are in the field of cell therapy, it has a lot more meaning than whether there is three steps or four steps or 15 steps. So I would like to offer that up to all the various constituencies here as a way of looking at manipulation.

I know the agency's interpretation is somewhat more on altering biological properties, but I think you have to fold that into it, and with that sort of prelude, I would like to bring up the idea, too, that in cases, for instance, in lymphocytes, and in our autologous lymphocyte therapy we have done extensive phenotypic analysis and functional analysis, some of which Dr. Noguchi and his people have suggested to us over the last four years, we literally have hundreds of patients in our trials where we have what we think is a well-characterized phenotype and a pretty well characterized -- I call it surrogate immune function, in other words, an in-vitro immune function.

So I would like to offer up to the agency the idea in terms of manipulation is that is it possible at some point of, let's say your level of satisfaction with the data, that if one merely augment what was considered to be a normal phenotype, and function of these cells, for instance, autologous lymphocytes restoring immune

function, couldn't that be considered minimally manipulated.

Maybe there would be an evolution from, let's say, more than minimally to minimally, but the whole concept is if a process is validated, well controlled, the product is well characterized, and we are basically doing something to the immune system that we understand, and that is, restore the normal function, and I guess I would offer up an example anecdotally in our own case, if I give activated or stimulated T cells to a patient with chronic hepatitis, and they clear the virus and seroconvert, the suggestion is you are restoring immune function.

So that is one concept I would like to put out and would like to hear any comments at the end.

The second one really relates to again this definition of homologous and non-homologous, and I think that the document does well in talking about structural cells and stem cells used for reconstitution here, but couldn't we consider here also metabolic cells, such as autologous lymphocytes in the homologous area since really if we can demonstrate normal functions being restored by these cells, why not consider them homologous at some point in time when the information is satisfactory.

So, those are two you can wait until I finish, but I would like to hear any comments you have on that.

The next area is really a reiteration of Ms. Raines' comments from Genzyme, and we have really similar concerns to Genzyme's in that general safety testing policy. As Dr. McKearn has mentioned -- I won't tell you the numbers -- we have processed a lot of patients and a lot of infusions, and no one has been contaminated.

The cells, however, have a 48-hour outdating. They lose their viability in their function. To go to a 7-day animal type general safety testing, basically, would have us reconfigure out entire process leading to really freezing of the cells, thawing of the cells, and then presumably loss of a lot of activity.

So the bottom line on that is it is really not practical for this autologous cell therapy to be under that type of regulation, so we would support Genzyme's position there.

The two other areas really aren't areas about definition, so you are not going to get too controversial, but one area we noticed in the regulations, and Dr. Bloom just gave me the guidance document and I haven't really read it thoroughly, is the area of supplemental indications that just came out on March 13th.

Our feeling is for cell therapies, there ought to be a well-defined carryover effect from one indication to another. So a suggestion here -- and it is probably easier to see in the CMC section of the BLA -- is that many of these cell and tissue processing methods are similar, if not identical, from indication to indication.

We would hope that the agency would exercise a great degree in flexibility, for instance, on an approved indication if basically the CMC sections are relatively similar or identical, if we could amend the CMC section, for instance, of the BLA, and just negotiate with the agency the type of clinical testing that would be necessary commensurate with the new indication.

My last topic, and probably the one I have the hardest time talking about, because it hasn't really worked out well, has to be the area of expanded access and treatment INDs. I know the agency has three methods - the expedited review, the accelerated review, and, unfortunately, I have the expanded access with the treatment IND to make these therapies available to large patient populations.

We appreciated very much getting the treatment IND in the fall of '95 for metastatic renal cell cancer, and Cellcor and Cytogen cannot really sustain on our own the cost of producing these therapies.

We would love to give them away, but it is not practical. Unfortunately, Medicare and almost all HMOs as a matter of policy do not reimburse treatment INDs to any degree at all.

We looked into that, and we don't feel that policy is going to change in the near future. Since the beginning of the program, which really started about a year ago, because we had to hire reimbursement people to deal with the insurance agencies because we couldn't do that with our own staff, we have only enrolled 20 patients in this program.

Over 70 were turned down essentially for financial reasons. Of the 20 patients enrolled, only 25 percent of them were able to get some reimbursement, and as all of you know, you are only allowed cost recovery, so we clearly negotiated with the patients, wanting to treat them, because in many respects, it gives us a much broader view of how the therapy may work in a real patient population.

The other factor, too, with the treatment IND is clinical sites do not want to deal with insurance companies, so out of the 24 or 25 clinical sites that participated in our pivotal and other studies, only about 6 sites are currently participating because they have the same difficulties and logistic problems in getting any

kind of real cost recovery, let's forget talking about profit.

So I think in the future, one thing that the agency needs to consider is that expanded access via treatment INDs is not really practical in terms of these more expensive therapies. We are not like large batch manufacturing companies that can make, let's say, 1,000 patients' worth of pills in a couple-kilogram batch.

Therefore, I would like -- and I don't want to be funny about this -- but I would like to think of expanded access really meaning expensive access, because that is the only way the patient can get the therapy.

My final comment really is just to continue to endorse the face-to-face interactions with the industry. I think they have been very good, and hopefully will continue. I would like to just state again the more clarity we have in these areas -- and we will clearly work with you to get that clarity -- the better it would be, and I also think that based on my first comments about definitions, that as these therapies become better defined, we need to think about moving them into other categories and be flexible about really where we place them based on their sort of safety and efficacy profiles that they demonstrate.

Thank you.

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MS. PENDERGAST: I have a question and a comment.

DR. MIESOWICZ: That would be very helpful. I know you have mentioned to help us before and we will take you up on the that.

MS. PENDERGAST: Yes; take us up on that because we think that treatment INDs are reasonable and necessary. But it raises the broader question of what is the drug-development paradigm that is keeping you in the treatment IND phase for so long. How long are you in the treatment IND phase before you do the studies that get you to the final approval stage?

DR. MIESOWICZ: Actually, I can answer that because it was very well defined by the Agency. They told us they would consider us for a treatment IND when we began a second confirmatory trial and finished accrual so as not to jeopardize accrual in that pivotal study. We were granted a treatment IND very promptly after that.

What is taking the time, really, is that our primary endpoint, as mentioned earlier, was survival and, therefore, one has to wait and would like to wait for a necessary number of events before you can file.

So one of the driving forces is the endpoints. I think the REGO initiatives with other endpoints being suitable for approval will minimize the time you are in a

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treatment IND. I have sort of been trying to think about mechanisms other than a treatment IND to help expanded access. I think right now it is all we have got, but no one is very cooperative.

My feeling is they are going to get less cooperative, not more cooperative, as more therapies come down the pike. So I think anything you can do with HCFA, particularly for serious and life-threatening diseases with only toxic therapies available, I think that would be very, very good. You could tier approach it there, too.

DR. SIEGEL: You asked for comments and I will comment briefly on a couple of issues. I think that our intent would be that lymphocytes that are used as lymphocytes to fight infection or tumor would be considered to have homologous function.

However, as currently defined in our document, if they were activated with cytokines, antigens or whatever, as you put it, albeit augmenting a normal function, that that would be considered not M&M, if you will--M&M with peanuts, maybe, more than M&Ms--although we are open and interested in further comments on that point.

I think you raised some very interesting points and a question regarding new indications. The document

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you have just received and not had time to read, which is one of the ones I had flashed up on the screen before, will deal with the clinical data requirements for new indications and will make it clear that we are serious about the fact that, in many cases, data regarding old indications will be useful in support of or substantiation of data for new indications making those newer indications easier to prove.

It does not address issues regarding, like, minor admendments to the CMC section, but I think that is a comment that we should take into advisement and discuss. It might well be that we can simplify the reporting and filing burden with those sorts of minor modifications. It is not something that we have addressed in this policy, per side effects, but we certainly can look at it.

DR. ZOON: I just wanted to make sure that people understand that those are still draft documents and that there is a comment period, so they are not final yet. Until they are final, those are not the operations of the Agency but, in principle, some of the considerations that are represented in those documents clearly are put out there for your comment and we seek your comment back on them.

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DR. SIEGEL: Right; although, as I was indicating regarding the MAS cell document, these documents--the effectiveness documents, to a significant state, and they will say where this is the case, represent an articulation of current thinking.

To the extent that they are consistent with, and, in our current thinking, they are up to--to the extent that they are new guidance. They are kind of hazy, a little fuzzy.

DR. MIESOWICZ: Thank you.

MR. GOLDHAMMER: Alan Goldhammer, BIO. I think I gave you a little easier last name to pronounce that go around. I guess my disclaimer is I am representing BIO. We have over two dozen companies, some of whom have spoken today, engaged a variety of cell and tissue therapies ranging from the mundane to the exotic including xenotransplantation.

I would like to commend the Agency with this Federal Register announcement and the accompanying document that clarifies a number of critical issues related to the cell and tissue therapy industry.

We are pleased that the Agency has considered a number of diverse applications of cell and tissue therapy in attempting to structure a framework for the oversight of safety and, where appropriate, clinical efficacy.

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As we understood, from earlier meetings with FDA, the central paradigm in creating this framework is the regulation of products with similar mode of action in a similar manner regardless of their classification. To this end, the FDA has generally succeeded. However, there still exists a certain ambiguity which, I think, we have all heard this morning and this afternoon, as to how certain cell products and processes will be treated by the FDA.

We agree with the Agency that the transmission of communicable diseases is a critical issue that must be addressed at both the point of collection and through any attendant processing steps that might be utilized.

As the complexity of processing increases, developers of these new therapies must be vigilant that the potential for transmission of disease is carefully controlled. The requirements outlined in this document are reasonable and are current industry practice.

Certainly, those products that require marketing application should have a CMC section that addresses product specification and processing controls. We look forward to assisting FDA as the good tissue practices, or GTPs, are developed.

As in the earlier document on somatic-cell therapy, FDA reiterates its position that the threshold

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for formal requirement of FDA approval is whether the cell or tissue is more than minimal manipulated. I am glad that somebody has come up with an acronym because I have had a great deal of difficulty in getting those words out unless I speak them very slowly. So I think I will start using M&Ms as well.

We have noted in past interactions with the Agency that this definition is problematic based on the past regulatory history of other types of procedures such as bone-marrow transplantation. While we welcome the establishment of the tissue reference group that will assist sponsors with questions about regulatory procedures, there continues to be this underlying concern with a variety of cell and tissue-therapy products.

It is stated in the document that the Agency would consider the processing of cells, both structural and non-structural, and non-structural tissues to be minimal manipulated when the process does not alter the biological characteristics of the cells or tissue,

Examples are provided to include cell expansion, encapsulation, activation or genetic modification. As is noted later in the document, this definition excludes the simple selection of certain autologous cells from a broader pool of cells.

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While we might agree that the directed genetic modification of somatic cells raises the issue of whether imparting a new function to a cell could raise novel safety issues that should be addressed, it is less than clear whether these same concerns arise from the expansion and/or activation.

The levels of the body's immune and blood system is in a constant state of variability depending on a variety of conditions. Lymphocyte counts can rise as a result of an infection. Hematocrit levels can rise as a result of altitude acclimatization.

If the same effect can be obtained ex vivo and those cells are reemplanted, is this not the same effect that might be achievable in the body, as Tom McKearn said. This is my central question.

We believe that this latter point warrants reconsideration. I think you have heard from some of the previous speakers on this point. So I will leave it at that.

Thank you for the opportunity to comment.

DR. NOGUCHI: Alan, in terms of the definition of more than minimally manipulated, what you are sort of proposing is those things such as actual genetic modification would quality but everything else wouldn't. How does that work into a company's sort of marketing

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advantage if, in fact, you fall into a situation where a premarketing approval would not necessarily be required.

How would you deal with that part of it?

MR. GOLDHAMMER: We have been wrestling with this problem, I think as you have, for the last year and a half to two years and trying to understand if one accepts the paradigm of changing the cell's function, or using--xenotransplantation is clearly, I think, an easier case to deal with although that is not on the table here.

But, for instance, is one is taking eyelet cells from a pig and implanting those into a human, we have said, here is a pathway that one needs the follow. If, however, we are taking cells out of a human, we are not changing the function of those cells. I think this is the question that we have been asking ourselves is should there be this formal regulatory approach.

Particularly, I think, as we have heard and I think Tom articulated it much better than I could, with regard to autologous cells where one is taking them out, the manipulations are argued to be minimal. Yet there is the thinking, at least right now, that there is some data that is just going to be needed.

I think, as I puzzled reading over to document within the last two weeks with all these other documents

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you guys have been giving us as well, which doesn't make it a lot easier, Jay, as you know--

DR. SIEGEL: It is even harder for us.

MR. GOLDHAMMER: It makes it even harder. You have made some cuts. You said that there were some areas that, at least a year or so ago, you were thinking that data would need to be supplied and now that is not the case anymore.

I think the stem-cell example is one that is well documented in this paper. I think that is why, when we look and say, okay, we are trying to treat like things alike, there is still some discontinuity in this document. But we realize it is an imperfect world and maybe that is, at this time, all we can do.

DR. NOGUCHI: If I could just follow up a bit on that. One of our concerns is that I think that the industry for cellular processing has established a very high level of--it is self-induced by necessity--GMPs and GTP equivalence.

Were some of these products to be downclassified where there is a matter of expansion, addition of growth factors and other sorts of things, we have a difficulty in seeing how an academic community would necessarily also follow the same procedures.

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That, I think, is part of the dichotomy that we are facing, that there are some areas we would like to back off on but there is also an inherent risk on growing cells of passing infections. Some of the orthopedic surgeons, as a matter of fact, are of the opinion that growing chondrocytes is relatively easy but doing it in a sterile fashion is a difficult thing and especially if you are going to do it more than once.

How would your proposal to downclassify a lot of things into minimally manipulated address that issue?

MR. GOLDHAMMER: I think there has been a paradigm for that in the transplant area where I think we heard this morning, at least there are some very good examples as to how it successfully has been handled through the use of standard setting.

I think that you are posing some good questions that we have been wrestling with. We have gotten this document out to our companies and we will be filing more extensive comments on the docket. I think what we will do is we will use that opportunity to expand on some of those thoughts.

DR. SIEGEL: In returning your thoughts to us, I would note, I think, Dr. McKearn pointed out very well that while the primary goal--well, this isn't what he would point out, but I would point out while our primary

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goal in drawing these lines was to figure out what made scientific sense, where regulation was important for the public health, an important secondary consideration is trying to draw a bright line.

As I am hearing you talk about changes that don't really change the cell function and then talking about things like expansion and activation which, of course, do change cell function, I am, perhaps, only slightly less perplexed than you are by what we consider a bright line.

I am simply suggesting that when you come to us with a proposal if, in fact, the bright line is simply whether you put a gene into it as opposed to a factor which may change the genetic structure or an antisense or wherever that line, the clearer you can be about what you think makes sense, the easier it will be for us to consider and, also, to consider whether it is a line that we can work with and identify and put out to provide some clear guidance.

MR. GOLDHAMMER: We will do that.

DR. SIEGEL: Eric, did you have a question?

DR. FLAMM: I was going to ask pretty much the same question. You had mentioned expansion and activation as not necessarily being more than minimal manipulation. So what I was going to ask is are you

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saying that there are some forms of expansion and activation that you would not consider more, or are you saying the line should be if something is added, it is more than minimal manipulation but if it is simply expansion or activation, you are saying no, it is minimal?

MR. GOLDHAMMER: I think that is a question that I will be glad to pose to the Tissue Reference Group.

DR. SIEGEL: I guess, in its extreme, you could take a bunch of cells and clone them into living organisms and say that was minimal manipulation.

MR. GOLDHAMMER: We are fully supporting cloning. Not to be flip, it is a question that we, ourselves, have been asking for the last two years. It is a very, very difficult question to ask. I think there are some examples that one could argue that you are simply replicating what goes on in the body.

That is why I drew those two examples. If you are expanding your population of cells, isn't that what your body does every day when you are insulted by one thing or another. To try to work within that paradigm is, I think, what we are trying to get at.

But, again, I think we have had the same difficulty in definitions as you have.

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DR. McKEARN: Could I, since my name was used a couple of times there, offer a consideration here? There was a time in the immunological literature about 1951 when small circulating lymphocytes were thought to be irrelevant to the immune response because they are in g zero, they are not dividing. How can these have anything to do with the immune response?

A number of Nobel prizes awarded since have established that they are the immune response. They are the immune response because those cells, in effecting their function, go through a predictable pathway involving replication, involving interactions with others, that are required in order to get the final function of the system.

So our point of view, not to necessarily ask BIO to adopt this, would be that the point of reference for evaluating whether this activation is good or bad is to consider what the normal metabolic pathway, in the usual sense of the word, is for that cell type.

As long as it stays within those boundaries, is that not exactly what you would expect and hope for in terms of providing that type of therapy?

Stated differently, if we took g-zero cells out and put g-zero cells back in, why would we expect to see any effect at all? So why do it? So that is the issue.

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We are afraid that you are comparing to the cells before they undergo processing as compared to after.

You should be comparing to the same cell lineage in vivo that is progressing through the normal physiologic process of an immune response.

DR. SIEGEL: I guess we would help you to answer the converse to that question, not why one might expect the cells unmanipulated would work but why one should expect that, once manipulated, they would, in fact, be effective for the treatment of disease.

DR. McKEARN: And the response to that is the literature. So look at what has been reported, what has been found and, obviously, we have been working very hard to develop additional findings.

MS. PENDERGAST: Tom and Alan, let me ask this question of both of you, then. We were trying to draw a bright line so that companies would know which side of the various lines they fell on and we wouldn't have to have another application system or any kind of thing where companies would have to come to the FDA and say, "This is what I do. What am I?" And they could get the guidance if they want to, but they wouldn't have to come to the FDA.

We are trying to limit the number of submissions. What I hear--and I don't pretend to

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understand the science here, but what I hear is people seem very uncomfortable with bright lines or everybody wants the line to fall just on the other side of wherever it is they are.

But the question is--you say, read the literature. I am saying that says to me, as a bureaucrat, that means that you have got to package the literature and give it to somebody at the FDA, they have got to read the literature and they have got to make a particularized decision.

What do you prefer, particularized decisions or bright lines even if sometimes you are going to fall on the "wrong side" of that line? How do you want us to play it, the big picture?

DR. McKEARN: There is another point that I think we have to remember and that is the need for flexibility. I think, had this meeting been held two years ago, it would probably be very likely that stem cells and selection would be on the other side of that line because we probably didn't know enough to make that cut.

Now, we have got some other things that, at least by this document, are still on the other side of the line. At some point in time, I guess what I would see is that now you have made some statements that this

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is over here now, maybe there are a whole bunch of things that, a year or two years from now, will be on that other side of the line.

That is another way to deal with it, that if there is a proactive statement on the Agency, to keep looking at it.

MS. PENDERGAST: That is our plan is to keep downgrading things and pushing them into the M&M, not the upgraded M&M with peanuts category, the more than minimally manipulated.

I guess the question is who is going to do the work? Who is going to do the packaging of that information and present it to the Agency so our Tissue Reference Group or whoever can say, "You know, you are right. Now that we see this and are comfortable with it, and it really isn't more than minimal manipulation. The cells are doing what we would have expected them to do. You didn't send them offtrack by whatever it is that you were processing--however you were processing them, you haven't sent them down the wrong course."

What is best way to do that, to, over time, have a capacity to downgrade. Will the one company that has already run the gauntlet of the more than minimal manipulation application be happy that we are downclassifying it?

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DR. McKEARN: We are probably not bright enough to be happy.

MS. PENDERGAST: Do you see what I am saying?

DR. McKEARN: Let me tell you what we have done and I will respond to your question with my question. So the response to this same question as posed in discussion with Dr. Noguchi was to generate phenotypes of a couple of hundred patients done a half a dozen times with a panel that fills the page. So now we have got somewhere in the neighborhood of 4,000 to 8,000 datapoints all in search of the rogue cell.

We are looking for the bad lymphocyte by phenotype or function that has arisen from this processing that could be argued to cause some untoward response in vivo, something that falls outside the phenotypes characteristic of cells as they march through immune responses.

So if we show you 8,000 negatives in a row, is that enough?

DR. SIEGEL: You are talking about the safety side. I think the efficacy side, if you were to refer to the literature, we have had--if you go back the last 12Êyears, there have been many--I guess I can't speak to how many have submitted to the Agency, but there has been

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a fairly large number of activated, expanded cellular therapies for cancer.

Not one of them has been generally adopted by the oncological community to date as an effective therapy. So, to make a general rule that since lymphocytes fight cancer and if you activate them and expand them, they will fight cancer better, that effectiveness ought not to be a concern, is one that I don't think the literature does, in fact, support at this time.

DR. McKEARN: The burden is on us to prove that we are inducing a specific immune response that augers to the benefit of the patient. We understand that. That is what the clinical trials are meant to support and we are happy to sit and present what we have to you. But that is how we put the trials together.

DR. ZOON: I guess I just want to expand on that one point as well because the issue that you have raised is if it does the same thing in the body. Our knowledge of the interactions of cells and various cytokines and growth factors present in the body is that a study that is of a complexity--that I am sure we will all agree that we don't know all the answers at this point in time.

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To say that we are mimicking something in cell culture that mimics the body, I think is suggesting the science is greater than where it actually is today.

But, in saying that, I think the Agency has been open to where there are standardized methods and standardized processes that an experience is gained for a certain type of product class and activity that we are willing to consider it in a different light and look at its ability to be downregulated.

So I think that, while I agree with you, I think the science is still evolving daily in the field of immunology and I think we need to just say that openly.

MR. GOLDHAMMER: There is no question about that, but one of the things that you can do and that you have done well historically is the holding of workshops. I would only go back to the safety-oriented workshops and the use of abnormal cell substrates of which I have been present, I think, at three of those over the last 12 years of where there was an extreme willingness to present data and to the point where a lot of safety concerns that were implemented in license applications 15 years ago are not concerns today and that I would suspect that we could arrive, in dealing with a lot of these things on a continuing basis, as well.

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DR. EPSTEIN: I would just like to comment that I am hearing from the industry side concurrence with the concept that there needs to be both process validation and clinical validation. I think that where the issue lies is whether the validation goes on on stage with FDA applications or off stage within the industry's self-determined mechanisms.

I think that what we are saying is that when you have manipulations that cross the threshold such that these kinds of validation are needed, that that is, in fact, the trigger for it being on stage.

I think that I don't hear a lot of disagreement over the kinds of studies or the kinds of data that really are needed in the case of cell expansion and activation.

MR. GOLDHAMMER: No; that's correct.

MS. PENDERGAST: Can I also make another point. The decision to limit the FDA's hard looks to more than minimal manipulated products, in part, arises from the fact that we have to triage where we put our work. It isn't as though there shouldn't be process validation even for less than maximal or minimal manipulation.

We just have a case that is soon to be written up in the MMWR of a tissue processing, a conventional tissue processing, that resulted in infectious tissue.

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So it is not that everything doesn't need good process validation and appropriate controls. It is rather that we are going to leave it to you. You get to self regulate when it is the easy stuff and we are only going to pay attention when it is the harder stuff.

It is the way of triaging and a way of recognition that there are limited resources and we are going to impose costs on industry commensurate with the risk and with the importance. But it is not to say as though there is a magic on-off switch in terms of the need for thoughtfulness and science and careful control.

It is just where we are going to devote our energy.

MS. RAINES: Lisa Raines. I just wanted to comment on the issue of the possibility of the possible downregulation of more than minimally manipulated products for which premarket approval is required and just suggest that that is a potentially very difficult thing to do if you want to preserve the incentives for innovation.

If you require a company to collect the clinical data, either before or after approval, at great expense, to allow competitors into that market without imposing on them a comparable responsibility and obligation, just as

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a policy matter, creates a great incentive to be the second guy instead of the first guy.

If you don't have first guys, you won't have second guys. So there really is a risk. I mention it in particular in this area because products that FDA considers to be more than minimal manipulated, those manipulations may not be considered patentable. Certainly, in the area in which my company is working, we do not have any intellectual property other than some trade secrecy with respect to our processes.

So, if there is no patent protection, if there is no FDA exclusivity as there is under the Food, Drug and Cosmetic Act for a period of five years for the first indication for a new drug, if you eliminate all of that in this area, you create a significant financial disincentive for companies to develop these therapies.

MS. PENDERGAST: A point well taken. That is why we need to hear back from you as to what you want. We are very curious as to which way do you want it. Do you want to preserve your confidential commercial information and use that as a tool, a marketing tool, and a market-entry barrier or do you want the Agency to be downclassifying as soon as it can things that, once we get a handle on their impact on the cell, the tissue and the body.

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So the comment period will be open.

MR. GOLDHAMMER: If I could just ask one final question. We support what you have done with the stem cells, but if you could maybe take a minute out, maybe two minutes, to give some thought as to how you arrived at that position.

DR. SIEGEL: That is for the next session, but one of the things that relates to this session that I think is relevant, to some extent, is the distinction between those products that are developed in a propriety atmosphere and those products that are developed by numerous individuals each with open sharing of data.

They do seem to lend themselves to different approaches and different incentives in terms of downgrading versus regulatory requirements and so forth. We have not formalized anything on that basis but I think that is part of the answer or thinking in that regard.

DR. FLAMM: I think it is worth highlighting, a distinction in downregulation that we have been using but not necessarily using very clearly. What we have anticipated, and clearly this could change, is that if we learn about a process, that the process, itself, does not alter the relevant biological characteristics of a particular cell or tissue, that would be downgraded, downregulated.

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It would not be more than minimal manipulation. But if we learn that you can reproducibly alter the biological characteristics by a particular process, that would not be downregulated per se. It would not be less than minimal manipulation. It is still more than minimal manipulation. It is just that you can do it in a reproducible way.

For that, what we would do is establish standards and that is something we will probably talk about more in the next session. So then, under the BLA, you could certify that you meet those standards. So you wouldn't be "downregulated," you would still need a BLA. But the procedure by which you would get that BLA would be much easier.

That would be something that would only occur if the industry decided that they wanted to provide the data to us in a nonconfidential form whereby we could set those standards. The stem-cell industry has indicated to us that they would like to do that but if you have a procedure that is not protected and that you don't think you are going to want to be used in a way to have these standards, then that is up to you.

So I think, in a way, we do have it covered in that if you want to be able to establish the standards and can give us that data, then we will be able to

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establish an easier way for you to meet the requirements without so-called downregulating.

DR. SIEGEL: This has been a very interesting discussion that would be fun to continue, but I understand and am pleased to hear that Dr. Robert Stillman has, as promised, arrived. I would like to introduce him, from the American Society for Reproductive Medicine.

DR. STILLMAN: Thank you very much. I sort of feel like the boy in the potty when the homework assignment was given out. I may have missed most of this morning and I very much apologize if I go over things that have already been covered.

As mentioned, my name is Dr. Robert Stillman. I am Professor of Obstetrics and Gynecology at the George Washington University and a reproductive endocrinologist who has served as the Director of the Division of Fertility and IVF Programs there for 18 years.

Today, I come to you as a member of the Board of Directors of the American Society of Reproductive Medicine who, I hope, in a disclaimer, will pay both my parking and my towing charge because the lot of full.

I want to start off by thanking the FDA and its staff for taking on a momentous task in trying to create a flexible framework for regulation, assuming that is

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diverse in nature as human tissue. I also very much appreciate accommodating my busy clinical schedule of cloning a few patients and trying to put the head of a lion on a horse.

ASRM has some technical concerns that I will detail in my comments but we are, nevertheless, very impressed with the depth and scope that the proposal has set out to date and I appreciate that you have sought feedback throughout the process and look forward to continuing to work with you.

Overall, we accept the proposed strategy for regulating reproductive tissues, albeit there is no such thing as regulation but, given the fact that there is a line somewhere to be drawn, and through general good tissue practices consisting of an infectious-disease screening and of testing and record keeping.

However, we want to seek clarification on some technical aspects of the proposal that I will detail. First, regarding transmission of communicable diseases. We understand that reproductive tissue donors, in most cases, will be subject to infectious-disease screening and testing.

Your proposal is similar to very long-standing ASRM guidelines in that we recommend very strongly infectious-disease screening--and it is almost ubiquitous

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now in the industry--and testing for anonymous donors of sperm and known sperm donors who are not sexually intimate partners of the recipient, or known to be sexually intimate partners of the recipient, followed by quarantining of donated samples.

However, we ask that you provide some clarity in requirements to "other" reproductive tissues. I give two examples, one oocytes and the other embryos. First, oocytes. There is no scientific evidence that disease transmission can come through an oocyte. It is not such as sperm where there is seminal fluid that can carry a virus but that is a minor point compared to the ability to screen and quarantine.

Currently, there is no clinical way to freeze oocytes and have them survive. So the idea of a quarantine is not available to us clinically today. So, first there is a no evidence of disease transmission but, much more importantly, clinically, it is impossible for us to freeze, quarantine and then use the oocytes in any effective way. It would be, in a sense, destroying the village in order for, perhaps, a need to save it.

Regarding embryos, while embryo cryopreservation is possible, quarantining of embryos by freezing them substantially decreases their viability and, therefore, their successful use later on.

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There is also, again, no evidence that disease transmission comes through embryos, especially if, as we already do, screen the gamete donors. In other words, the semen donor and the oocyte donor are screened themselves and, yes, it is an embryo but, of course, it comes from those gametes and those individuals are screened beforehand.

So, to quarantine embryos, you would substantially either decrease the success rate of the procedure on one try or have to do it many more times and, therefore, markedly increase the costs to the patient for this clinical applicable procedure.

Therefore, we would really ask that you consider eliminating the quarantine on oocytes since it is just not a feasible thing to do from a scientific point of view and strongly urge that you eliminate the quarantining of embryos because of the marked decrease in viability once they are frozen compared to a fresh embryo.

Secondly, we would also suggest changes in some of the labeling practices as outlined in the proposal. We believe that your intent is that banked semen and embryos are labeled so that inadvertent infection can be avoided. We agree with that intent.

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However, reproductive tissues, the labeling requirements described would be somewhat problematic because, in fact, actually the straws and vials used for reproductive storage are extremely small and it would just really be an issue of how literally to label them.

We would ask that we work with you to determine a feasible way to classify the tissue samples in the categories you suggest but going along with the labeling requirements for such a small vial.

Thirdly, with the same labeling requirements and concerns in mind, we also seek clarification on the destruction requirements. Should this proposal become a regulation, is it the FDA's intent to require programs to destroy embryos and semen stored prior to the labeling requirements or would the programs be required to relabel thousands of frozen samples frozen prior to the regulations.

A concern here would be the possibility that removing them from cryopreservation, just to label them, would seriously compromise their potential for future use. We urge you to rethink any retroactive labeling strategy for reproductive tissues including the exempting of tissue cryopreserved before regulations going into effect.

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I hesitate to use the word "grandfathering" in such a--again, we would be happy to work with you to determine a more effective way to deal with these tissues.

Fourth, clinical safety and effectiveness; one of our greatest areas of concern about your proposal lies within M&M, and more than M&M. We ask that these definitions be further clarified. Previous discussions with Ms. Pendergast indicated that manipulation of reproductive tissues in in vitro fertilization is considered minimal manipulation; that is, it does not alter the biologic or relevant functional characteristics of the tissue or cells.

With this, we agree. We certainly appreciate the understanding of the special nature of reproductive tissues because, in fact, sperm in an egg becoming an embryo is somewhat different but it falls within the guidelines and on "our side" of the bright red line.

However, the definition for other medical treatments for infertility is not as clear cut and we hope that they can fall on our side of the red line by being made clear. An example would be a promising infertility treatment called assisted hatching where an opening, a small opening, is made in the outer shell, the

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zona, of an embryo to enhance its capability of implanting.

Some might argue that, in the wordings of the regulation, this procedure alters the biologic characteristics of the embryo by enhancing its implantation. Yet, as a medical procedure, it should not be considered more than manipulation and, if it was, it would require testing and marketing approval for this medical procedure.

Other examples abound; intracytal plasmic sperm injection, coculture systems for immature oocytes that can be retrieved less expensively and more easily, but require a little bit more in vitro culturing, where, along the line, does this fall.

We are particularly concerned that if regulations are not further clarified, you would, indeed, be regulating the practice of medicine in clinical, applicable circumstances. I think this is a far cry from what we understand is the intent of the regulations.

Although these remarks that I have brought up today raise some concerns and suggest changes and certainly ask for clarification, I want to reiterate our appreciation for your efforts and our desire and willingness to work with you to resolve these issues that I brought up today.

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In summary, the quarantining of oocytes which is, really, just scientifically not feasible today, the quarantining of embryos. Number two, labeling, including vial size labeling. Three, the retroactive destruction or labeling and its problems regarding reproductive tissues. And four, and particularly, the minimal versus the more than minimal requirements as it applies to clinically applicable procedures.

On behalf of the ASRM, I want to thank you for this opportunity and, again, apologize for going out of turn. It has been a problem I have dealt with since I have been a little boy.

Thank you.

DR. SIEGEL: Thank you. Dr. Stillman, since you weren't here this morning, I would like to ask you, as we did some of our other speakers--I think that it will be very helpful and informative to us, particularly on this issue of minimal manipulation, to receive from you and your organization to our docket a listing of examples such as you started to give us of types of manipulation that are going on and what the arguments would be, why they ought to be considered in different ways. I think that that will help us provide more clarity. I appreciate that.

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DR. STILLMAN: We would be pleased with the opportunity to do so, including some that clearly would fall on the other side of the line.

DR. EPSTEIN: Thank you, also, Dr. Stillman.

The group that has been developing standards related to reproductive tissue is aware of many of the concerns that you raised. I guess it has to do with fine print. For example, with regard to quarantine control, there is a footnote that says for allogeneic tissue that can be stored. What we meant by that was where that would not compromise the integrity. That is a general principle that would be applied to quarantines.

So we don't envision forcing people to quarantine things that would become useless if they were held.

DR. STILLMAN: I didn't have to be here today, then?

DR. EPSTEIN: Regarding the labeling, it, of course, has been pointed out that one cannot label the straws. But we think of labeling as all the documentation. Certainly, there are records that could accompany the straw. That would be labeling and that might be where the information resided.

The straw, itself, might have either nothing on it or just its ID number or a color code. We don't

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really expect volumes of donor information to be on a straw.

I think that the inventory problem will take more thought. We appreciate that remark. Likewise, I agree that we could spend some time thinking about more than minimal manipulations. I would just echo Dr. Siegel's comment that you could be very helpful to us explaining manipulations that you think we ought to regard as minimal manipulations.

DR. STILLMAN: Especially given his remarks, which I very much appreciate, there is nothing in the regulations from our particular society, and I can't speak for others and so on, which, with rather simple discussion, as you have fostered before and here today, could not be resolved to our satisfaction.

DR. SIEGEL: We are a little behind time. However, we have--did you have a question? If anybody has prepared cards and would like to pass them down.

MS. BACQUET: This is Cathy Bacquet from Chiron and Viagene. I just wanted to address Lisa Raines' comment about differentiating between allogeneic and autologous. I just wanted to make the point that allogeneic isn't always bigger in batch size. Take the point where you have bone-marrow transplant and then you

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give them the lymphocyte donors to reinfuse those bone-marrow transplants.

So, essentially, you have got an allogeneic process that is almost autologous in that there are chimera. I don't know if you get the point, but--so, again, you may be making a lot size that is specific for the patient even though it is allogeneic and the lot size might be very small.

Again, you have this problem with testing that was brought up for the autologous. I would make that point. Thanks.

DR. SIEGEL: We will take a 15-minute break and reconvene to discuss stem-cell therapies. Please be prompt. We are a little behind.

[Break.]

Stem Cell Therapies

DR. SCRIBNER: Welcome to the section on stem cell therapies. We have seven speakers who have requested time. We are going to lead off with a short presentation by Dr. Liana Harvath from the Office of Blood, Research and Review, followed by the seven presentations. We will keep everybody to ten minutes with an extra five minutes for questions, if necessary.

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We already have one question coming from the floor, if Mr. Rosen decides he doesn't want to stay. Then we will continue with the program.

Are there any questions before we get started? Very good.

Dr. Harvath.

FDA Introduction to the Issues

Clinical Safety and Effectiveness

DR. HARVATH: I would like to thank all of you for attending this meeting and for your continued interest in the area of hematopoietic stem and progenitor cells. I would also extend thanks to those groups who have invited us to participate in your recent scientific conferences during the past week.

As many of you may know, there was a Leukemia Society of America meeting here in Washington D.C. and then a recent international workshop on cord blood in Indianapolis, Indiana. We had the occasion to present the policy and the proposal to both of those meetings.

What my assignment has been for this afternoon is to overview some of the salient features of this proposal as they pertain to hematopoietic stem-cell products. What I will do is, some of the information from this morning but the purpose for presenting it is because I have received some feedback from groups who

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have expressed some concerns or areas that need clarification.

So, to stimulate that discussion further, I will bring those points up.

[Slide.]

As you heard this morning, for the testing, there will be required testing for all allogeneic donors. Dr. Periera outlined this to include HIV, HCV, HBV, HTLV, CMV and syphilis and that there will be a required screening for all allogeneic donors to include a high risk for HIV and hepatitis, Creutzfeld-Jacob disease and tuberculosis.

The reason I am presenting this is because there have been some concerns raised by some professional organizations regarding how to handle CMV positivity in the way that that should be presented on the product labeling.

So we would appreciate your comments and suggestions regarding that issue and also some others have question as to why a screen in the medical history to cover tuberculosis. Again, we would invite you to present to us data or suggestions of alternative proposals to do this or whether these are warranted.

As you have heard previously, we are going to recommend testing for autologous donors to include HIV,

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HCV, HBV, HTLV and recommend screening for autologous donors for high risk of HIV and hepatitis. Thus far, we haven't received too many comments questioning this although some have asked why don't you make requirements for testing instead of recommendations.

So if any of you feel strongly about that and have data to support such a proposal to us, please feel free to write that to the docket. As you know, our proposals with hematopoietic stem and progenitor cells have been occurring since December of 1995 when we first held a public workshop. We cosponsored with the NIH on cord blood stem cells.

Since that time we have had the discussion be a very open and iterative process in trying to obtain input from all interested parties regarding this particular type of cellular therapy.

[Slide.]

Now, in the fine print of Table 2, and some of the fine print has already been pointed out to you, but we have requirements in one of that footnotes. The reason I am putting this slide up again is that a number of transplanters, over the past year and a half, have expressed to us their extreme concern that FDA would mandate any position that material or even test negative from a potential high-risk donor that we would

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automatically eliminate that and prevent any transplanter from using that.

The reason we put this up is to let you know that, in fact, if the following requirements are met, then these products will not need to be destroyed from the inventory. That is, if a product is labeled biohazard or untested for biohazard, if autologous cells that are collected clearly are labeled for autologous only, also written, advanced informed consent of the recipient is documented so that if a transplant physician chooses to use these materials, that this will be one of the criteria that we feel very strongly is important.

Finally, there needs to be documented knowledge and authorization of the recipient's physician. So, if these criteria are met, the transplanters will be able to use the material.

[Slide.]

In the next slide, processing controls; you heard about this with Dr. Solomon's talk this morning. The terminology of good tissue practices relating to contamination, integrity and function including handling, record keeping and labeling procedures.

She mentioned one set of standards from the AABB. I would like to also mention that there is another set of standards that were not mentioned. Those are the

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FAHCT standards. There is a set of standards from the National Merit Donor Program. What we encourage all of these organisms to do is to continue with their dialogue with us, to submit their standards to the docket, to work together to try and come up with a cohesive set of standards that where there are subtle or somewhat little minor differences that, perhaps, if you could work them out as a group, present them to us, that would make our job much easier.

We have appreciated working with many of you and receiving the comments and concerns that you have had. I think, by seeing the listing of examples of good tissue practices, you could literally go through these standards and see that these, in fact, mirror what are called good tissue practices.

There will be, for those products that fall into the M&M category, and for those of you who might now know, we in the agency also use that term, that more comprehensive processing controls than good tissue practices to address clinical safety and effectiveness concerns would be required for cells for unrelated allogeneic use.

This is where you are talking about where something now becomes a GMP. This was explained very well this morning so I won't draw on that point.

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[Slide.]

Clinical safety and effectiveness; data will be required for four circumstances which have been detailed before, and that is cells from an unrelated allogeneic donor, cells that are manipulated, cells that are used for other than their normal function, or cells that are combined with non-tissue parts.

What we will do in the next slide, because the question of what is manipulation, comes up. It has been discussed extensively in the previous session, but as pertaining to hematopoietic progenitor cells, we have found that the two areas that clearly we feel, because of lack of data and lack of data for engraftment and durability of the graft would include cells that undergo ex vivo expansion and gene insertion.

For those of you who may have attended these meetings in the last week, at the Leukemia Society of America and at the International Cord Blood workshop, it was very clear that most of the scientists who are in this field are very uncertain as to the engraftment of ex vivo expanded hematopoietic stem and progenitor cells.

So there is some very interesting biological data that are unfolding at this point and many of them, I think, are in unanimous agreement that there needs to be a study for safety and effectiveness in this area.

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[Slide.]

Processing standards; what I would like to do in the next few slides is to walk you through the FDA intends to promulgate establishment controls, processing controls, product standards for hematopoietic stem cells. We have written in the proposal that we intend to invite professional groups and individuals to submit their data to the agency and standards that they believe would insure safety and effectiveness for these products.

From some of you, we have heard, in previous meetings, that we know these work. We just know. It has been published in the New England Journal of Medicine, we have this experience. So what we are going to do is to invite you to provide that clinical data, those scientific data for the product characteristics and for the way that these cells should be processed and handled.

You will be reading in the Federal Register in the future the invitation to submit those data and you will be given a sufficient period of time to be able to compile those data and present them to us.

If, after that time, there are not sufficient data available to develop processing and product standards, then the stem-cell products would be subject to IND and market application requirements. This will be a phase-in with ample notification of this process.

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[Slide.]

A little bit more about standards development. I mentioned that we will list in the Federal Register some relevant questions for developing the data and standards. Again, during this open comment period to the docket, we would love your input. For those of you who are very knowledgeable in this field, who have a lot of hands-on experience in the cellular aspects of these products as well as how to screen, process, store, ship these products, we would love to hear what your concerns are and what you would like to see in our question list that goes out to the public.

Examples that came to mind in our internal discussions include the criteria for an acceptance of a unit such as volume, storage temperature limits, microbial and other contamination limits, viable cell number, functionality, procedures for handling, transporting, storing and thawing these cells.

Another feature not put on this slide but which is also very important is when do you think these procedures should be performed. Should they be performed at the time you have collected the unit and committed that unit to be stored in the bank or should they be performed, let's say, concomitantly with the time that

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you are going to release a unit and use it in a transplant.

That is something we would be very interested in hearing from you.

[Slide.]

Finally, product labeling and advertising; you have heard from many people that we feel very strongly it must be clear, accurate, balanced and non-misleading. Many of you in this room know that, in the cord-blood area, this has been a major problem. This has been something that the agency has received a lot of concerns, comments, and requests for help.

We would also like to hear from you what you think represents fair, accurate, non-misleading labeling of these products. This morning, there was a very good example of a speaker who said, "We think labeling should include how these cells were processed, outdates if there are known." That kind of information would be very good to know.

Other things may be including the experience of the bank performing these procedures, anticoagulants, you name it. But we would like to hear what you think would be fair and accurate and non-misleading.

On that note, I would like to take a scientific prerogative to use a very famous scientist's quote. It

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is on the wall of my laboratory. It is something I look at every day. Professor Carl Sagan, as many of you know, recently passed away of myelodysplastic syndrome. He, himself, was the recipient of the bone-marrow transplant.

These words have impacted me so much and I thought that they were very relevant, particularly to the promotion of material where we may have a hope that it might work but we don't yet maybe have all of the data necessary to make a promise.

He said, "How rigorous the standards of evidence must be if we really are to know something. How many false starts and dead ends have plagued human thinking. How our biases can color our interpretation of the evidence. How often belief systems, widely held, turn out to be not just slightly in error but grotesquely wrong. Everything hinges on the evidence. The more we want it to be true, the more careful we have to be."

On that note, I will turn this over to the chair of the panel.

DR. SCRIBNER: Thank you, Dr. Harvath.

We will now continue with our first speaker. We have Ms. Cynthia Fisher representing Viacord.

MS. FISHER: Hello. My name is Cynthia Fisher. I am president and CEO of Viacord, Inc., in Boston, Mass. I am here to talk to you today about the proposed

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regulations and give you a little bit of background about Viacord.

We are primarily a related allogeneic cord blood bank as most of the families that bank with us bank primarily for a need or risk or desire to bank newborn child's cord blood for potential use by another family member.

We do have some families that bank specifically for autologous reasons, but it is a very small proportion of those that bank with our service.

I would like to take the opportunity today to talk about the development and the history of the proposed regulations especially as it relates to stem cells. I certainly commend the agency because, as you can hear from the conversations and from the issues brought forth today and the issues for all tissue, whether it be structural or from stem cells, they are quite complex and intellectually stimulating as we think these through.

It has certainly been a challenging task for the agency and I commend that the agency has put forth these proposed guidelines in a relatively timely fashion based upon the complexity of the issues.

Pertaining to the field of stem cells, we commend the agency for its new and innovative and

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flexible approach toward the regulation of human cellular therapy and human tissue therapy.

We also support the oversight and jurisdiction by this new Tissue Reference Group to put in place a streamlined approach, more or less funneling questions concerned and put in place consistent policy and review for all of the human cellular and tissue therapies which apply.

We support the tiered approach and also the five-point approach that has been explained and mentioned earlier today. This tiered approach provides a framework that most apparently can address those therapies, critical therapies, that have been brought forth to the agency to date but I think, importantly, is a structure and a framework which will apply to therapies that are yet unknown to us.

Most importantly, as we look at this newly proposed regulatory model, we are looking at its ability to provide broad access to patient families for these critical transplantation therapies, especially as we see as it pertains to stem cells and, at the same time, enabling such broad access, the agency has put in place a model that makes sense to fully protect public health and safety, specifically that of the infectious-disease

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testing and good tissue practices and record keeping and appropriate guidance on labeling.

These protections that have been set forth can ensure such protection. We support the accountability that labeling and promotion can be held to be both accountable for its accuracy, its balancedness and its responsible presentation.

Also, significantly, we feel that timely implementation and implementation of the guidelines as they have been proposed in an expeditious fashion can better insure and better protect public health. Through these measures that have been proposed, the public can be better served.

I thank you for this time to present. I commend the agency for this significant undertaking and the guidelines that have been proposed and, basically, commend the complexity that has been involved. To patient care, most importantly, this is an enabling framework for today's therapies and access to those that will be developed in the future.

Thank you.

DR. SCRIBNER: Thank you, Ms. Fisher. We much appreciate your comments. Are there any questions for Ms. Fisher before we go?

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DR. HARVATH: Cynthia, I would like to ask a question. We have tried to get the landscape of use of cord blood transplants in this country because they are not required to be reported. We wanted to ask all of the speakers the same question and that is, in your cord-blood transplant program, how many units of cord blood have actually been used in a transplant and whether they have been for autologous, allogeneic-related or allogeneic-unrelated.

MS. FISHER: Liana, as I had mentioned earlier, our bank provides primarily for private family banking. Our focus has been for related allogeneic potential use and them some autologous use. Specifically, answering your question about the number of transplants, we have had one transplant to date that has been undertaken through our service, since we offered or service as of August of 1995.

We have incorporated and did research and development studies from June, '93 until '95, but starting in August. The one transplant was transplanted last May. We do maintain a registry of outcome and do have that indicated in the patient record and maintain ongoing tracking.

Fortunately, it was a seven-year old leukemic who is now eight and doing quite well. I just spoke to

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her transplanter about two days ago. But we do keep that on file and I guess are you specifically asking about the registration of outcomes, Dr. Harvath?

DR. HARVATH: I was wondering if, perhaps, you may have reported it to the IBMTR or any other transplant registry that usually captures cord-blood data.

MS. FISHER: The transplanter himself fully intended, and to my knowledge, has reported to the IBMTR as he gave us the outcome data consistent with the IBMTR format.

DR. SCRIBNER: Any other questions?

DR. EPSTEIN: Could I get you to comment about the concept of a registry for allogeneic stem cells? Would you participate and how do you see it relating to directed donations, first, non-family donations?

MS. FISHER: Viacord's viewpoint, as we had submitted to the docket earlier, was supporting that of registration of transplant outcome and, as I said, we have it on record for each--and we will continue to do so--for each one that our bank is involved with.

I think on the bigger issue, as far as how outcomes would be recorded and to what agency, as I know there is the IBMTR or to those in the audience that are not familiar, it is the International Bone Marrow

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Transplant Registry, there is also now a Cord Blood--Dr. John Wagner is registering cord-blood transplants.

And then there is also, now, I understand that the National Marrow Donor Program is thinking and, possibly, even the CDC for epidemiology. So I think I would choose to defer to the bone-marrow transplanters, specifically FAHCT, the Foundation for Accreditation of Hematotherapy and Hematocellular Therapy, and also the American Society for Blood and Marrow Transplantation because I believe that the transplanters are the best to determine how they would see such outcomes of their transplants and to what agency and how this mechanism may work, and I would defer to their advice.

DR. SCRIBNER: Thank you very much.

Our second speaker today is Emily Rossiter representing Thermogenesis.

MS. ROSSITER: Thank you very much, Dr. Scribner. CBER is to be congratulated in its preparation of a well-thought-out proposal of the agency's intended phase-in of the requirements and regulations of cellular and tissue-based products.

The document is comprehensive, well written and easy to understand and is a reasoned approach to the evolving regulatory oversight of these emerging technologies. Thermogenesis agrees with most of the

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contents of this document. However, we would like to make a few comments for agency consideration and enter them into the docket for the record.

Mr. Phil Coelho is the president of Thermogenesis and, by the way, this document has been prepared by Dr. Michael Zmuda who is the vice president of regulatory affairs and quality assistance of Thermogenesis.

The exclusion of cellular and tissue-based products involving close blood relatives or related allogeneic donor-recipient pairs from the IND, premarket application and GMP regulations seem poorly justified.

CBER indicates on page 10 that the exclusion would be handled as a policy matter. I think we had reference to that earlier today and, on page 13, offers the rationale that "the agency believes that it is appropriate to leave it up to the family and their physician to decide whether to use such tissue and would not prohibit use even of contaminated material from closely related donors."

Thermogenesis believes that, if implemented, such an exclusion would seriously confuse the evidence that is required to evaluate the utility of this emerging technology and would create an uneven playing field or other similar allogeneic products.

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It is not possible, at this time, to comment on the safety of autologous hematopoietic stem cells derived from cord blood. To the best of our knowledge, the transplant of autologous cord-blood-derived stem cells has never been attempted. However, with regard to related allogeneic stem-cell transplants, it is not clear how the agency will be able to fulfill its obligation to protect the larger number of family members who could be so treated and whose safety could be compromised by lack of what we consider to be appropriate developmental oversight controls.

Further, it is also not clear how enforcement of the IND and premarket regulations would prevent a family and its physician from deciding to use a related allogeneic product even if contaminated. Instead, it would seem these regulatory processes would help establish strict guidelines and criteria for safe and effective related allogeneic use of cellular and tissue-based products.

On page 21 of the proposal, CBER states that inadequately controlled or otherwise improper processing of products can result in ineffective and unsafe therapy, giving as an example, nonviable stem cells used for hematopoietic reconstitution after chemotherapy. Thermogenesis strongly believes that the absence of

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appropriate IND premarket and GMP controls significantly increases the risk of inadequate and consistent, poorly controlled and potentially hazardous collection, processing and cryopreservation and storage procedures being applied to these cellular products.

Safe, effective and standardized methods have only begun to be established by researchers at the New York Blood Center and NIH who intend to document their findings under INDs. Based on promotional information recently published by one of the commercial operations collecting cord-blood donations for potential future related allogeneic use, many thousands of samples have already been banked since 1995.

The absence of IND premarket application and CGMP controls over the eventual possible transplant of these several thousand samples stands to significantly confound what should otherwise be a clear and better controlled evaluation of these new technologies.

According to CBER's own proposed rationale, these new techniques may, with appropriate supporting data, enhance and expand the use of human cells and tissues as therapeutic products.

On page 19 of the proposal, under metabolic function, CBER states that the agency believes some autologous and family-related allogeneic uses or

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hematopoietic stem cells may have an established history of safe use. The promotional information published by the commercial operation referred to above indicates that a collection and mailing kit is provided to the expectant mother and that is her responsibility to take the kit with her at the time of delivery so that the cord blood may be collected.

It goes on to indicate that the sample must be shipped by overnight mail and received at a single U.S. facility within 22 hours of collection. Thermogenesis is not aware that any published laboratory or clinical evidence exists which demonstrates that impromptu collection of cord blood by staff in the delivery room, shipping under ambient conditions by air express to a distant facility and subsequent processing, crypreservation and storage results in a viable, non-contaminated stem-cell suitable for transplantation.

Among a number of apparently unsubstantiated claims, the promotional information goes on to state, "Samples banked at," the name of the company, "have been successfully used for both related and unrelated transplants in established hospitals and centers across the country."

Although this statement gives the impression of a widely successful program with countless successful

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transplants, the current worldwide number of transplants from stem cells derived from cord blood has barely exceeded a meager 400. Nearly all the stem cells for these transplants have come from IND approved cord-banking operations at the New York Blood Center.

Thermogenesis is unaware of any peer-reviewed journal articles of transplanted stem cells that have been banked with the commercial operations cited above and wonders what the real number of successful transplants might be. We believe that the agency may be unwittingly presuming viability and effectiveness of commercial preparations of related allogeneic hematopoietic stem cells.

In the promotional materials cited above, cord-blood donation is made simplified, safe and the right thing to do and commingles the world transplant experience with the unsubstantiated track record of this particular commercial operation.

For example, over 300 cord-blood transplants have been performed around the world and thousands of families have taken advantage of this new technology by collecting and storing their baby's cord blood in case of future need. Another quote; "Dozens of patients have already been saved by the cord blood from their newborn siblings and many more families have privately banked

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their babies cord blood as a form of biological insurance in case of future medical need."

There is no discussion of the risks inherent in the cord-blood collection and transplantation processes nor of the fact that few, if any, of these 300 transplants were carried out with stem cells banked from the company's vault. Further, this is no disclosure of patient outcomes at 90 and 360 days for any transplant performed with this company's cord-blood deposits.

Finally, the information does not disclose the fact that there are currently no documented standardized methods that have been universally accepted for subsequent handling to insure that stored stem cells will be viable later on when needed.

The only reference to government regulatory compliance is a statement indicating that all reagents used in processing are FDA approved. Consequently, and because of the runaway commercial interests involved, Thermogenesis supports the agency's proposed requirements for clear, accurate, balanced and non-misleading labeling.

However, we strongly believe that without an IND and premarket application rules, FDA will have no systematic way of regulating the labeling and promotional materials of these enterprises.

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In conclusion, Thermogenesis believes that commercialization of related allogeneic hematopoietic stem cells should raise a very high level of concern within the FDA. It would, therefore, be appropriate to regulate commercial operations which have been established to prepare cryopreserve and bank such related allogeneic products.

We further believe that one, proposed requirements for compliance with establishment registration, listing, good tissue practices and adverse-event reporting regulations are insufficient to the absence of IND, GMP and premarket application controls will lay open significant health risks on an important segment of the population, those family persons who may receive related allogeneic stem-cell preparations and, three, ultimately, clear and convincing demonstration of the clinical utility of these products will be significantly confounded and the best interests of the public can only be served by a playing field which is level for all allogeneic stem-cell recipients, whether these come from bone marrow, peripheral blood or cord blood.

Therefore, Thermogenesis recommends strongly and supports the inclusion of IND, GMP and premarket application requirements in the regulatory plan for

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commercial operations which intend to market related allogeneic stem-cell preparations.

We further strongly support FDA oversight and enforcement of the labeling standards as stated in the proposal and we have included in this letter to the docket some specific labeling and informed consent elements that we feel will foster fair, accurate and non-misleading labeling.

Thank you.

DR. SCRIBNER: Thank you, Ms. Rossiter. You have certainly brought some very sobering thoughts and ideas to our discussion and we will be very interested in looking at the submission to the docket for complete review as we respond.

Are there any questions for Ms. Rossiter? Any comments?

Thank you very much.

Our third speaker is Dr. Rebecca Haley representing the American Association of Blood Banks.

DR. HALEY: I am Dr. Rebecca Haley. I am the senior medical officer for the American Red Cross. I am the Chair of the AABB Hematopoietic Cellular Therapies Committee. The American Association of Blood Banks has 800 institutional members. This represents most of the

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blood collection and transfusion that is done in the United States today.

This organization writes standards and oversees the collection and processing and transfusion through those standards through voluntary cooperation of its members. The AABB sincerely appreciates inclusion in this process and the public opportunity to comment.

The AABB basically supports the proposed tissue regulation especially in the development of cord-blood banking. This new approach combines the flexibility to permit access to the rapidly expanding therapies and the rigor to insure that safety and efficacy concerns are satisfied.

Thus, we are pleased that the FDA is proceeding on a fast track to develop regulatory structures. As new processes and technologies become available, the demand for their use increases dramatically. There is a clear need to have appropriate regulation without delaying access to available treatments.

After reviewing the proposed regulation, however, we wish to note a few issues that bear further consideration. These involve distinctions between autologous and allogeneic uses, flexibility to allow electronic labeling, regulation of advertising claims, appropriate tests, inclusion of bone marrow within the

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progenitor-cell standards and use of professional standards as a certification method.

First, let's talk about private and public cord-blood banks. As drafted, the FDA document identifies an unusual distinction between autologous and allogeneic use of cellular and tissue-based products. Autologous homologous use in oral presentation appears to include transfers between close blood relatives and/or sexually intimate partners.

The usual definition, of course, of autologous is limited to the use by the donor only. Perhaps the distinction should be drawn between banking products for private restricted use and banking of donated products for the general public.

Careful consideration should be given to explaining the distinctions drawn in the proposal and to clarifying the differences in the proposed regulation of products intended for autologous and family use and those stored for unrelated allogeneic use.

To the extent that entities engaged in autologous or reserved collection, storage and processing activities seek to offer services to an unrelated allogeneic context, it should be clear that the increased regulatory requirements and scrutiny will apply.

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Labeling; the regulations regarding labeling should be carefully considered. Electronic on-site labeling is part of the basic technology associated with blood collection, processing and distribution. It can be expected to be a practical necessity in the collection, processing and distribution of cellular and tissue-based products as well.

Any labeling requirements should be flexible enough to permit the use of electronic labeling.

Promotion and advertising. Following Ms. Rossiter's presentation, this seems very small but, given the intense public interest in the new developing therapies associated with these products, issues concerning advertising claims can be expected to exceed those with which the FDA biologics groups may have been familiar in the past.

It appears, although it is not clearly stated, that the Tissue Reference Group identified in the proposal will review the advertising claims. We agree that all promotional claims must be accurate and supported by scientific data.

The authority of the Tissue Reference Group should be clearly defined. In addition to reviewing advertising claims, the group should have sufficient

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authority to insure that misleading statements are removed from the marketplace.

Testing and screening. The proposal has identified a series of required testing screening procedures which, in some cases, are inconsistent with current medical practice requirements for blood and blood components. This is part of the issue that Dr. Harvath discussed earlier.

For example, the proposal requires anti-CMV testing of allogeneic products but misses the point that the appropriate action to be taken regarding the anti-CMV results is a simple labeling of the unit as CMV-positive or negative without biohazard designation.

Given the frequency with which CMV occurs in the donor and in the transplant population, it would be inappropriate to require donor deferral or biohazard designation, the same as you would for other transmissible disease tests.

We believe the privacy of some donors may be compromised by a proposed a labeling requirement which we read into the Table A2, Table 1, as proposed autologous or related tissues as cellular units would be labeled with the test results. Currently, blood components that are tested positive in the autologous domain are labeled as biohazard with the specific test result confined to

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the medical chart and not included in the label. This preserves the privacy of the donor or of the family member and we would recommend that process for the labeling here.

The requirement for the medical history relating to tuberculosis should be reviewed and clarified to limit the application of this requirement to medical situations for donor and/or recipient for the risk of tuberculosis transmission is known to occur; for example, in bone grafts.

GTPs with respect to the application of good tissue practices, it should be noted there are a series of inconsistencies with the proposed regulatory scheme. As GTPs are finalized, they should be revised to conform with this proposal. For instance, there is no mention of P24HIV antigen testing and there are very clear differences in the number kinds of questions and the limits on the kinds of questions that are asked.

We expect GMPs to apply to units collected for the unrelated allogeneic banks, as do you, but we are concerned that GTPs and GMPs are not the same and that the people in the blood-bank world are used to working with GMPs and may have difficulty changing theirs to GTPs and wonder if that is a good thing.

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Inclusion of bone marrow; the FDA should consider including the collection, processing and storage of bone marrow in this proposal. Although the collection process is very different, among the three sources of progenitor cells for bone-marrow reconstitution, the cellular product, hematopoietic stem cells and the uses for the product are the same.

In our standards, the processing and storage controls for the three sources are held in common. Consideration should be given to including bone marrow in the same basic oversight and regulatory process.

Standards: the AABB endorses the concept of using uniform industry standards in lieu of INDs to insure content and safe practices. The AABB has already developed standards for stem-cell collection, processing and storage on a cooperative basis with the foundation of accreditation of hematopoietic cell therapy fact.

The AABB believes that the uniform standards can be adopted and would be pleased to participate in this process. Private organizations can conduct inspections in a self-regulatory process but we have no enforcement authority. The AABB suggests that careful consideration be given to developing a program that provides the FDA with the appropriate enforcement authority while allowing

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the self-regulating agencies the necessary flexibility to act.

The AABB would welcome the opportunity to discuss this concept further. Above all, the AABB applauds and wishes to participate in the FDA's effort toward a unified approach toward regulation encompassing traditional blood products as well in the future and other cellular and tissue-based products.

Thank you.

DR. SCRIBNER: Thank you, Dr. Haley. Those are very good points. I believe Dr. Harvath has some questions for you.

DR. HARVATH: Becky, I wanted to ask the same question. We were going to limit the question to cord blood and not peripheral blood because we know the numbers for peripheral blood stem cells are in the thousands. But in the experience of the AABB and Red Cross, have your organizations participated in collecting units that have been used in cord-blood transplants yet and, if so, were they for a related allogeneic or an unrelated allogeneic?

DR. HALEY: The Red Cross is in the research phase that Ms. Fisher described that preceded her collection phase. But we probably will be collecting soon. So that is not an issue for us.

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With the AABB, I think most of the allogeneic unrelated transplants have been included in the registries that we mentioned before. We do not have any AABB members that I know of and my knowledge is not absolutely complete that have collected inside the family or have a family-based bank.

DR. EPSTEIN: I have one question about hazard labeling. You seem to be saying two different things. On the one hand, for CMV, you would like CMV-specific labeling whereas for other positive infectious markers, you would prefer that there not be specific labeling.

DR. HALEY: That's correct.

DR. EPSTEIN: Can you explain that?

DR. HALEY: Well, probably one reason is because that is our practice now and it seems to work well. If you know that someone is HTLV-positive or hepatitis-B-positive and that is labeled on the back, then if that word gets around, if this is seen, that can affect their future insurability and can affect the way that some of the people around them treat them.

We figure that this is an invasion of privacy. CMV, on the other hand, is a very different analyte. It is different because it may be important in the CMV-negative recipient who has no antibodies and has not had prior immune exposure, but, in the general population,

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only when they are in the immunocompromised phase, in the general population and in the CMV-positive patient, it really doesn't have a relevance.

So, that is why. And the reason that I know that this can be a problem is that if you put biohazard on it, the nurses on the unit refuse to hang the unit because we have done that with apheresis platelets. We were given a very ugly red label that said "Positive for anti-CMV." And we were sending it for CMV-positive patients.

The nurses were refusing to do this awful thing to their patients. So I think that this is not clinically relevant to try to place that kind of importance on it as not helpful. On the other hand, I think it is probably an invasion of privacy.

DR. EPSTEIN: I believe the proposal is not actually to put the disease-specific marker on the label, just as a point of clarification, but I think we will certainly consider your remarks about CMV.

DR. HALEY: Thank you.

DR. SCRIBNER: Other comments?

DR. RUBINSTEIN: Briefly, with respect to CMV in particular, this infection is unusual and illustrates one of the most peculiar parts of infectious-disease reasons, in the case of cord blood. Because the serologic status

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of the mother and the baby depend on the infection of the mother but not of the baby, the presence of antibodies in a specific baby are not portents of the capacity of that baby to transmit the infection.

The issue is not whether the mother has been infected in the past and, therefore, has serologic influences, but whether the baby has the virus. There are, therefore, aspects of the regulation that are specific for cord-blood transplantation and the standards should reflect these aspects. We will refer to these in my own comments later on, but I think the issue of CMV is critical to this problem.

DR. HALEY: I certainly agree.

DR. SCRIBNER: Thank you for the clarification.

Other questions?

Thank you very much, Dr. Haley.

Our fourth speaker today is Marie Staie representing the International Cord Blood Foundation.

MS. STAIE: Good afternoon and thank you. On your agenda, you did see the listing of Dr. Paul Billings. Unfortunately, he was not able to attend today and he did request that I extend his apologies. He was called away unexpectedly.

So, with that, allow me to introduce myself. I am Marie Staie, Director of Donor Services at the

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International Cord Blood Foundation. Dr. Billings probably would have covered a different area than I intend to cover, probably much broader. But since my position at the Foundation is the screening and consenting of the donors, that is the area I would like to cover.

ICBF is a not-for-profit corporation which was founded in 1995 with the mission to increase public awareness about the benefits and the uses of cord blood to create an allogeneic cord-blood bank from volunteer donors that would supplement the existing marrow donor registries and to attain further knowledge of the use of cord blood through research.

We would like to commend the FDA in their effort in making the regulation of human tissues user-friendly. The proposed guidelines will continue to protect public health and safety while leaving flexibility for advancement in patient treatment.

I would like to encourage the agency to keep in mind, while finalizing these guidelines, the differences in organizations, the collection models and unique situation of cord-blood donation, the ability to be highly selective from as large number of potential cord-blood donors will result in the highest quality and

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safest stem cells to be delivered to the ultimate recipient.

Currently, we get calls from expecting parents from all 50 states interested, very interested, in donating. Being able to provide the option of donation to a parent, no matter where they are located in the country, instead of a selected few that deliver at specific hospitals, gives us a wider basis from which to select the very best based on family health history, ethnic background, and low risk factors.

We believe that our ability to collect cord blood from such a wide geographical area would better enable us to establish a more ethnically diverse donor bank of the highest quality. And the question I had in mind was the timing of the consenting, testing, of the maternal blood and quarantine issues.

Those were the facts I was referring to. I am short and sweet today because I have a flight to catch. So that will be it.

DR. SCRIBNER: Thank you very much.

Dr. Harvath?

DR. HARVATH: The same question. How many units from ICBF have been transplanted and have they been for allogeneic unrelated or allogeneic related?

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MS. STAIE: All of the foundation samples are for allogeneic unrelated and there has been one.

DR. HARVATH: Did you report that to a scientific journal or IBMTR?

MS. STAIE: I believe so but I would have to double check on that because that was before my existence with the organization.

DR. EPSTEIN: You suggested a concern about the timing of consent and the timing of collection but what, exactly, do you propose?

MS. STAIE: We currently consent our donors. We start the consent process with no less than 60 days left in the pregnancy. We believe strongly that the moms have the right to be informed of their different options for their cord blood and have the right to choose to donate or to start by themselves, not happen to be the lucky one that delivers at the right time with the right staff on duty.

DR. SCRIBNER: Are there other comments?

Thank you, Ms. Staie. Good luck on the dash to the airport.

MS. STAIE: Thank you.

DR. SCRIBNER: Our fifth Speaker today is Thomas Moore representing Cord Blood Registry.

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MR. MOORE: Good afternoon. Although we intend to submit full written comments for the record, we appreciate the opportunity to be here today and tell you briefly about our company and a comment on the proposed framework.

Cord Blood supports the regulatory approach set out in FDA's framework and would also like to add our comments in thanks to the FDA in striking a proper balance between protecting public health and safety and encouraging research and development of this exciting, promising technology and allowing private banking to progress.

[Slide.]

I quote what we consider the cord blood birth model up on the screen. Today, there are about 4.3 million births a year in the U.S. The majority of those births are discarded in terms of the cord blood. We believe the model breaks down into two sides, ones that I would refer to as high risk and the other side which I would refer to is the lowest risk.

The low risk is typically the area where we would like to see cord blood saved. And, over at the left-hand side, are typically the type of clients that Cord Blood Registry serves and those are either the very high risk patient or a high-risk category in general, or

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people who would just like to say--and I think Cynthia Fisher pointed out that basically her cord-blood model probably follows somewhat the same as that.

So we focus on those two red dots over the left-hand side. We believe the agency properly distinguishes between the requirements for autologous and same-family use and allogeneic use. We agree that the FDA should not try and intervene in medical treatment decisions related to same-family use.

We also agree that being concerned about communicable disease is important and we concurrently conduct, on all of our cord-blood samples, the tests recommended by the FDA and more. Cord Blood Registry looks forward to working with the AABB and FAHCT and other groups to establish good tissue practices which insure the purity, integrity and function of stem cells.

[Slide.]

It is important when establishing these standards, however, to ensure that they do not unnecessarily restrict patient access to collection by creating unnecessary GTP requirements. Today, CBR has over 2,000 doctors that have collected samples. That has taken place in over 1100 different birthing hospitals throughout the United States and it represents, roughly, about 6,000 samples that have been collected.

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We agree that it is useful for the agency to determine its inspectional requirements based upon whether an entity is certified by FAHCT or AABB. Cord Blood Registry distributes fair, and we feel accurate and balanced, promotional materials and will work with the industry to establish guidelines on promotion.

In closing, Cord Blood Registry appreciates the seriousness with which the FDA has addressed these issues and looks forward to participating actively with both the agency's rulemaking and voluntary industry standard-setting activities.

Thank you.

DR. SCRIBNER: Thank you, Mr. Moore. We certainly look forward to your written comments when they come in for our evaluation.

Dr. Harvath?

DR. HARVATH: Mr. Moore, could you tell us how many transplants have been performed with units stored at CBR?

MR. MOORE: Yes. We have been actively storing units since November of 1995. We have presently provided two transplants. One was done it late November of '95 and the second one was done three weeks ago.

DR. HARVATH: Were those family related?

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MR. MOORE: Yes; they were family related but, in all cases, they are sib transplants. Most currently, a transplanter will not transplant an autologous sample within two years. There have been no private banks prior to two years ago. Therefore, no autologous transplants have ever taken place.

DR. SCRIBNER: Other questions from Mr. Moore?

DR. HARVATH: Did you report your data to the IBMTR? I have to ask everyone the same questions.

MR. MOORE: Actually, our protocols do require the transplant physician to do that. The protocol also has reporting back to us at three months, six months, 18 months and then each year thereafter for five years.

We also, however, have reported to the international group.

DR. SCRIBNER: Excellent. Dr. Rubinstein, do you have a comment?

DR. RUBINSTEIN: It is a question. Last week, in the Indianapolis meeting, the same question regarding the number of transplants done by CBR or supported by them was asked of Dr. David Harris who was in the audience at that time. He made some comments. He said there have been four transplants.

This illustrates, in my opinion, the necessity for these numbers to be documented in a completely

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reliable and unambiguous fashion. The principle method that we now have for measuring transplant usefulness is the outcome data since it is not possible to evaluate the number of stem cells. For this evaluation to be possible, we must have data on outcomes of all the transplants performed.

So I wish you could explain to us about this discrepancy and suggest how we can, in the future, orient ourselves to regarding decisions.

MR. MOORE: I think the discrepancy between two and four has to do with Dr. Harris' bank that we acquired. We acquired that bank in 1995. Prior to that time, he did to a transplant, two transplants, and provided two samples. One was transplanted by Dr. Wagner and the other was in Minnesota, and the second one, I believe, was transplanted by Michael Graham in Tucson.

So they were before Cord Blood Registry acquired the bank. I was referring to the samples since we have acquired the bank and that we have privately stored.

DR. SCRIBNER: Thank you for the clarification.

MR. MOORE: Thank you.

DR. EPSTEIN: I just wanted to inquire what standards do you follow? Do you follow any published industry standards regarding the collection, processing, storing, thawing, et cetera?

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MR. MOORE: Industry standard; let me first talk about infectious-disease markers because I believe that is probably where, if I was to say there were industry standards, that probably comes closest to standards which are the blood banking standards. Typically, all of those samples are tested for infectious-disease markers that are more rigorous than what are in the current regs.

In terms of processing standards, there were standards that have been set by the bone-marrow--or people who have processed cells for bone marrow for a number of years. There are also samples that have been processed with cord blood such as Dr. Rubinstein's in the New York Blood Bank uses which is the second method that has been used.

Principally, we have used both methods. We don't find that the yield is as good using the starch method of Dr. Rubinstein's and since we privately store, in some cases, it is very important to get the highest yield possible.

Our yields are typically running about 95 percent and I believe 95 to 98 percent, in that range, in terms of the cell viability.

DR. SCRIBNER: Thank you very much, Mr. Moore.

Our next speaker is Dr. Elizabeth Schpall representing the Foundation for the Accreditation of

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Hematopoietic Cell Therapy. Oh; excuse me. We have a change here. I see Dr. Nancy Collins coming to the fore to present this information.

DR. COLLINS: Good afternoon. Dr. Schpall was unable to come because of illness in the family. And I send her regrets. I am from Memorial Sloan Kettering. I am laboratory director of the allogeneic stem-cell facility there.

Today, I am speaking to you in my role as a member of the Board of Directors of FAHCT which is the Foundation for the Accreditation of Hematopoietic Cell Therapy, and its two parent organizations, the International Society for Hematotherapy and Graft Engineering, or ISHGE, which is the professional organization for stem-cell collection and processing facilities and the American Association for Blood and Marrow Transplantation or ASBMT which is the organization for clinical stem-cell transplantation.

Today, one of those three organizations is going to buy my shuttle ticket.

Over the past two years, we have developed standards for stem-cell collection, processing and transplantation and FAHCT will, within the next month, launch our inspection and accreditation program.

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FAHCT and the agency have had multiple formal and informal meetings over the past five years. We believe this has been a learning experience for both parties. We also share the concern of the agency regarding certain current practices in stem-cell collection and transplantation. We applaud the agency in seeking to create a new paradigm for regulation in this area and we do appreciate all of the effort which has gone into this document.

The Board of Directors of FAHCT has performed a preliminary review of the document and we have submitted it to the proper committees of FAHCT and our two parent organizations, ISHGE and ASBMT, for closer consideration. You can appreciate that before we submit our official opinion, we want to make a very careful examination of the proposal that could not be completed in the very short time period between its release and this meeting.

As a matter of fact, at lunchtime, I was talking to someone and I was saying, "This is sort of like peeling an onion. Every time you look at it, there is another layer to go through." So we are working at this very carefully.

We believe that FAHCT and the agency are in agreement on the advantages of the uniform approach to tissue regulation. We feel that there are real

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advantages in their tiered system of dealing with issues of infectious-disease and submissions to regulators. We feel that the inspection and the accreditation program that we have developed is exactly what the agency has requested of the transplantation community.

The FAHCT standards are the considered opinions of the most knowledgeable scientists and clinicians in the field. Indeed, the field was built by those who wrote the standards. This group includes not only researchers at the cutting edge of science who are aware of the ambiguities and facilities of the field but also the people who have built the commendable and very well controlled systems in blood banking, our partners, the AABB.

It has not been easy to reach a consensus but we have come up with a rigorous set of guidelines that both assure the safety of the stem cells being transplanted and, importantly, allows space in which research can be done. We have established a class standard in consultation with the other professional organizations, as I mentioned, the AABB, the NMDB, the AATB.

As a matter of fact, there is considerable cross-fertilization because the members on one committee are the members of the organizations of the committee. Our document is already a model for our colleagues in

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Europe and elsewhere and it contains all of the elements of GTP as outlined earlier today.

However, we feel that there are certain aspects in the proposed regulatory approach that are not scientifically sound and some that might impede the progress of research. The issues are now complex and the proposed scheme takes into account in certain areas and sometimes do not fit well within the proposed IND formula.

I would like to present just a few examples of the concerns which we have with this document. First, FAHCT is concerned that requiring the use of the IND mechanisms for grafts derived from this specific source will severely limit the quantity of research and the swift application of new knowledge into the clinical setting.

We absolutely support safety and controls over experimental techniques being applied to patients. Let me say that once again. We absolutely support safety and controls over experimental techniques being applied to patients.

We have controls built into our standards. The IND mechanism, as we understand it, is designed towards the production of product insuring that it is the same every time. There is a place for this system but not

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based solely on the source of hematopoietic cells. The challenge is to define at which point a technique ceases being experimental, at which point an IND is required.

We fear that premature freezing of techniques by complying with the present IND requirements will mean a slowing of the pace of research and our ability to use the best new techniques and knowledge.

Secondly, the document also contains some language that we are uncomfortable with. For example, related transplants within a family do not occur only between first-degree relatives. We believe that when a cousin or a grandparent or an aunt or an uncle is the donor, the risk of the transmission of infectious disease is not significantly different than when the donor is a parent or a child or a sibling.

We are also troubled by the difficulties introduced by determined regulation by the intended use of the stem cells. Specifically, we are concerned with the homologous/non-homologous definition. We are concerned with the definition of the use of stem cells in certain metabolic diseases, like metabolic storage diseases, as non-homologous. In these diseases, the stem cell is the vehicle for the delivery of a normal enzymatic pathway.

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Lastly, we also have some questions which we will outline further in our written presentation and our written submission by April 17 about how ancillary devices and reagents that we use in processing. We will present our other concerns when we file or official response by April 17.

Perhaps, the combined wisdom of the larger group of scientists and physicians that comprise our group will devise imaginative ways to address these problems and others.

Let me say again that FAHCT and the agency share real concerns. It is in our own best interest to build a safe and credible system that will both protect our patients and allow them to benefit from the best science we can offer. We believe we can work together towards this goal. We thank the agency for listening to our concerns. We plan to continue this dialogue.

We appreciate the new model and we feel very strongly that we can work within its framework.

Thank you.

DR. SCRIBNER: Thank you, Dr. Collins. As we have for the last five years, FDA looks forward to continuing to work with all the experts in the field to discuss the issues.

Dr. Harvath, do you have a question?

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DR. HARVATH: Nancy, I have to ask you the same question. I know ISHGE has done a transplant so I know there has been one place where there has been a transplant of a cord blood in Colorado. So, knowing that there is one, I am wondering are there, within FAHCT, ISHGE, your group of people who are putting together the comments to the docket--can you tell us how many of those people have done cord-blood transplants or that have come from a cord-blood bank that they have set up?

DR. COLLINS: I don't want to hazard a guess on that because it would be a guess on my part. What I would like to do is I will refer that to John Wagner who is the head of the Cord Blood Committee and who is keeping track of this. I know we have done a handful at our center. There has been a handful done here and there, but I really don't want to go on the record with a number.

DR. HARVATH: The other question is what is your position on the reporting of data to IBMTR?

DR. COLLINS: Within the standards, we encourage the reporting of data. There was great discussion as to whether we would require it. We decided not to require it after all last March when we went over the standards, but would definitely do encourage it.

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One of the underpinnings of all of the standards was looking at outcome data. I mean, that is the one thing on which we build everything else for the reasons which Dr. Rubinstein said, for that is how we know a graft works. So outcome data goes back all the way into the collection process.

DR. NOGUCHI: Thank your for your comments. I would just like to respond to two of the areas in terms of flexibility under INDs. I would just point out as the division that really deals with the 351 types of categories, I can assure you we have been extremely flexible with the types of experiments that have been going on.

And so if that is the primary concern, I wouldn't list that very high. I suspect the concern may be something else.

The second is the question of the non-homologous use vis-a-vis stem cells and correction of a metabolic defect. For the types of things that we are talking about, these are the ones that are being attempted in utero, not in a born individual, in which, quite frankly, we have now three of those under IND. The standards there are there are not standards.

The dosing is not clear. The effectiveness of the procedure, itself, is highly variable and, in

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general, we feel that, for that particular situation, in utero, you are asking stem cells to do a whole lot more than just repopulate the hematopoietic system.

There have been some reported successes. There have been some reported failures. It is one area that we feel fairly strongly should, at this point, be under IND.

DR. COLLINS: Thank you for that comment. That is what I mean about the onion analogy. Every time we look at this, we think of things in a different way. That was not at all a part of our discussions when we had a conference call and when we went over the proposal. It is a 28-page proposal which is going to take a bit of time for us.

We will continue the dialogue about the IND because we are concerned that we be able to have a protected research space in which we can change a buffer, we can optimize, continue to optimize. And we know that you have been sensitive and, from our very first discussions with you, we have heard of improved INDs, fast INDs, and we know that you are sensitive to our concerns.

MS. PENDERGAST: With respect to your onion analogy, we refer to our program as conceptually robust.

DR. COLLINS: Thank you.

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MS. PENDERGAST: Help me understand something. I don't understand why you feel that the INDs slow your research. Other areas of explosive scientific growth seem to manage quite well under INDs. What is it that you see as the big problem with INDs? Is it the form? Is it the failure, if you are under IND, that you are not going to get your research paid for by the patients?

What is the issue for you?

DR. COLLINS: I think the issue here goes back to the fact that we don't know whether a processing or change in the manipulation works until a patient engrafts. So we can do a lot of preclinical in vitro testing. We can take a small part of a peripheral stem-cell harvest and I can work on it in a number of ways and I can go through CD34s and I can measure clonogenic units.

I can do a lot of things with that but it isn't until I work on an entire graft and I put an entire graft into a patient that I know whether it is going to work or not. This is very scary. This is very scary and so we do a lot of preclinical testing before we do it on the big one.

So we sit down and we do it on the big one and then we say, "Have we done it the best way we possibly can? Is there another buffer?" See, there is a great

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difference in working with a very small bit of bone marrow or a very small bit of peripheral stem cell compared to working with a large amount.

These are very difficult to come by. There is a difference in physics. There is a difference in the concentrations. There are all sorts of biologic parameters which are different. What we are concerned with is if we are required to have an IND before we do that first patient, and that first patient doesn't work, or doesn't work as well as we want it to, and we say, if we change this buffer or if we change that part of the procedure, maybe we are going to get what we want.

What are we going to do then? Are we going to then have to change our IND for the next patient? What are we going to do? Perhaps this is where the dialogue with the agency is going to tell us that we needn't worry about this.

MS. PENDERGAST: Let me push a little on that. So you are doing it and you don't know if it is going to work until it engrafts. You have done your preclinical work and then you finally do the big one with some patient.

If I were that patient, wouldn't I feel like this was an experimental therapy and maybe it was going to work and maybe it wasn't going to work? And, if that

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is the case, then don't you see the value of the IRBs and informed consent and all the other patient protection things that there are around INDs.

DR. COLLINS: Those are already in place.

MS. PENDERGAST: So it is not the informed consent, patient protection.

DR. COLLINS: No. The informed consent and the IRBs are built into the standards and are absolutely and integral part.

MS. PENDERGAST: So that is fine.

DR. COLLINS: Definitely.

MS. PENDERGAST: And you already know what you are planning on doing and you have outcome measurements to see if it is going to work. So the clinical protocol part is fine.

DR. COLLINS: Right.

MS. PENDERGAST: And who pays for it? Is that part of the problem here? Do you want the patient to pay for it or do you think your research institution, since you are experimenting, ought to be paying for it?

DR. COLLINS: I can't answer that right now because this is something which I think we have to--I realize that this is an underpinning of your concern. You have mentioned it in very many meetings. I will refer that back to our greater committee.

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MS. PENDERGAST: I just want to narrow down because if it is paperwork, if it is what is the breadth of the protocol I can write and get approval on, we can negotiate with you on that and I think Dr. Noguchi sort of explained that.

If it is the whole concept of an IND that you don't like because it shifts who pays, then we need to know that because we can't negotiate. Do you know what I mean? No amount of negotiation by Dr. Noguchi over how the IND is written is going to solve that problem.

So it would just help us if you could be very, very explicit as to what it is about INDs that you don't like and why you think that IND, in and of itself, would slow research. I would appreciate that.

DR. COLLINS: I will take that back to the greater committee and we will put that as one of our--

MS. PENDERGAST: Great.

DR. ZOON: I also had a similar comment because the very things that you seem to elaborate on are clearly the issues that would normally come under an IND and that there is a lot of flexibility in the submission of information and the generation of knowledge under an IND.

So I am also a little confused about what the problems are that you see or that you face because the

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more specific you are, the more we can sit down and work with you regarding those issues as they may arise.

Secondly, I feel compelled to ask this question after Liana has asked the question to several people. My observation is that there has been a limited number of cord-blood transplants. I guess I would ask your organization, who is developing the standards, do you truly have enough information to develop standards and how do you know you have what is important?

DR. COLLINS: I would say that that part of our standards was written and headed by John Wagner and Joanne Kurtsburg. We think that we have gone to--Dr. Rubinstein has been invited for his comment. We have gone to every recognized cord-blood transplanter in the country. So we think we have gone to the best.

DR. SCRIBNER: Does your standard also include mechanisms for adapting or changing as the knowledge changes?

DR. COLLINS: Definitely.

DR. EPSTEIN: I would just like to clarify. You have made clear a point of view about the IND but the proposal is for a phased requirement where we would allow a reasonable period of time for the industry to develop voluntary standards for processing which would then serve in lieu of the IND.

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So are you, in fact, therefore, comfortable or uncomfortable with the proposal? We have said no IND now, and you have gotten up and said, "We are against INDs." But you haven't, then, clarified where you are with the proposal which says we will allow industry a period of time to develop standards in lieu of the IND process.

DR. COLLINS: We are very pleased with that section of it. I almost wish I could have just said yes to you. No; we are very pleased with that part of the proposal but, once again, I would like--I'm sorry; this is intellectually robust. This is an intellectually robust proposal and we are looking at it.

We are happy and, as I said, we can tell that you have heard us. We hope that we are hearing you and we hope that we are hearing you correctly.

DR. SCRIBNER: Other questions?

Thank you, Dr. Collins. As my colleague, Dr. Cavagnaro, said, perhaps using your onion analogy, we now understand why some people on the other side of the bright line are crying.

Dr. Rubinstein is here representing the New York Blood Center.

DR. RUBINSTEIN: I am grateful for the opportunity to speak before this panel. Unfortunately, I

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have to bring forth a message of disagreement with the decision taken by FDA not to require an IND across the board. The reason for this unhappiness on our part is that the IND mechanism is the only way that guarantees that all the information that we generate in the course of the initial period of application of this technology will be available for evaluating its potential for good and bad.

Specifically, about the new document, I would like to focus on the development of standards and the consequences of the development of standards. The aim is, obviously, as it is stated in the document, to ensure the safety and efficacy of the products.

Because at the moment there is no method of identifying the one element of the transfer which is causal to the recovery of hematopoiesis in the patient, it is not possible to define this at the moment. All of the information that we generate is based on surrogate tests. These tests need to be performed in special ways and evaluated with respect to a large number of variables that impinge on the outcomes which are currently the sole way to determine the success or failure of the therapy.

The problem in applying knowledge to the generation of standards is extremely serious in a therapy where the safety and efficacy in a certain sense are

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synonymous. The patient with complete aplasia receives a cord-blood transplant. If the transplant doesn't work, it is both a question of safety and a question of efficacy.

For these reasons, it seems that the precise documentation and reporting of the findings that will be made, it is essential in the process of developing a safe and effective therapy.

The consequences of these situations are fundamental also in the issue of autologous and family-related transplants. At the time of collection of the unit in the close family circle of potential patients, if we understand the document correctly, at the time of collection, it is not necessary to follow a clinical protocol approved and part of an IND.

But these units may be used in the context of something more than minimal modification and manipulation later on. The companies that perform these services advertise that it is possible, for example, to predict that in the future it will become feasible to introduce genetic material into these cells.

Will the agency clarify for us whether this statement of minimal manipulation applies also in a prospective sense. In other words, if that is so, all of

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the tissue that has been collected at the moment without an IND would not be permissible to modify in the future.

A similar situation applies to the labeling. Obviously, if it will not become possible to use this material for future manipulation and changes, these should be well known by the patients who grant their informed consent for the preservation of tissue in this fashion.

A specifically difficult point in this connection is the consequence for the advertisements that focus on available knowledge obtained in a different way. The standards that will be developed will, hopefully, obviate this problem only to the extent that the problem, itself, is well understood.

If an article representing a company who will process tissue for family use uses, as the intellectual foundation, the existence of data proving the usefulness of the transplant in a completely different realm, this should be presented clearly to the potential client.

A final comment addresses the issue of the desirability of the IND in view of my very good friend and colleague, Nancy Collins. It has been our experience as the oldest cord-blood bank in the country, that the obtaining of the IND only facilitated our flexibility in contemplating technical modifications to protocols since

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it gives us an opportunity to discuss them and to make sure that all of the necessary safety issues are considered in these modifications.

So far, our experience has been superb in getting the support and help that we need.

Thank you very much.

DR. SCRIBNER: Thank you very much, Dr. Rubinstein.

Dr. Harvath, your questions?

DR. HARVATH: Dr. Rubinstein, could you tell us how many cord bloods from the New York Blood Center have been used in transplants from your bank?

DR. RUBINSTEIN: Yes. There have been 357.

DR. HARVATH: What is your feeling about a centralized place for reporting the outcome data. We have been talking about IBMTR because, as you know, John Wagner took his database and is sharing it now with IBMTR. Where would you feel the appropriate place for reporting that would be?

DR. RUBINSTEIN: We have a slightly different view of this ever since we have our IND. We feel that it is our responsibility to collect and maintain the information from all the patients who receive our transplants. First of all, we must make the data available to you, the agency.

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Secondly, from the scientific point of view, we feel that we are really the appropriate group to conduct the complete evaluation. We have no objection to share to our data with IBMTR and with other agencies. The European cord-blood group, for example, with whom we met last week in New York after the Indianapolis conference, was in complete agreement with the necessity for the development of technical standards as opposed to general standards which have been proposed by other agencies, technical standards that represent the state of the art in the cord-blood field, itself.

The development of these standards are, by necessity, dependent on the quality of the information on which they will be based.

DR. HARVATH: I had one more question and that is about elaboration on your recommendations for CMV testing.

DR. RUBINSTEIN: We believe that studies of CMV should be addressed directly at the presence of virus in the material or in the child who is the donor. As we understand it, current state-of-the-art in CMV investigation uses as a gold standard the viral culture.

Viral cultures are most often positive in either urine or saliva. It has become our policy to do saliva cultures. It may be, in the future, possible to

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facilitate this process since we have identified that in every single case thus far, the mothers have synthesized CMV-specific IgM antibody. So upon a thorough discussion with the agency, we hope to evaluate the possibility to simplify the standard and just use the IgM or to replace the viral culture by some type of molecular amplification technique done directly on saliva, infant saliva.

DR. SCRIBNER: Are there other questions for Dr. Rubinstein?

Thank you very much.

DR. RUBINSTEIN: Thank you.

DR. SCRIBNER: In spite of my promise to Dr. Confer who I suspect has already left, we are late. We have one question from the floor. We have two questions to Dr. Noguchi. Why don't we start with the one from here.

Dr. Zoon or Ms. Pendergast, would you like to address that question?

MS. PENDERGAST: I think it has been answered already.

DR. SCRIBNER: It is all taken care of. Okay.

Dr. Noguchi.

DR. NOGUCHI: These are two issues related to some of the comments today. The first one is in regard that, in many cases, the FDA would not require data to be

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submitted directly to FDA but it would need to be available upon inspection. The question is at what point and what would prompt FDA to inspect a company that did not need to submit data to FDA.

I think Ms. Pendergast addressed this briefly this morning that part of the process, we hope, is to engage the professional organizations and other standard-setting bodies to assist us in inspections. I think those who choose to not be certified by such bodies, as has been mentioned before, certainly might raise some suspicion in our eyes.

We have heard actually today some reports of advertising which certainly would be another type of trigger that would enable us to really focus in.

I think one of the things we need to think about is by distributing the responsibility over several different layers, we hope that this will enable FDA to really focus in on those what we might call outlyers who really don't seem to play by any of the rules. Those are the ones that really give the industry the bad name. We are trying to, also, get away from the concept that if you are regulated, then everybody has to jump through an extra amount of hoops even though the person you want to get doesn't jump through any.

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So I think that is sort of the approach that we are taking. Certainly, anybody else is welcome to add to that.

MS. PENDERGAST: I would just like to add the point that one of the reasons why we have a hard time accepting the notion that if you are in a trade group or you are accredited, then, therefore, the FDA should disappear completely is because we don't want to be in the position of basically compelling people to belong to groups that they otherwise wouldn't want to belong to.

So we have to be careful about people's associational interests as well.

DR. NOGUCHI: The second one is actually very related to Dr. Rubinstein's previous comments. If a company were to have a product that is cell based and would not necessarily be regulated now by FDA, I would change that to say, all companies will be regulated. It is really whether or not a premarket submission is required.

But if it goes beyond the manufacture of the cell product and then, at some future time, decides to use these cells for gene transduction as an example, at what point in this process would the GMPs be applied; at the beginning of transduction or back at the beginning of the cell-therapy product?

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Technically, we would say that the GTPs that are being proposed would be a subset of what would be required for any 351 type of product or an FDNC type of product. But the GMPs are also phased in; that is, normally, under product development, you start out with not necessarily complete GMPs before you have your plant and your establishment fixed.

But we expect you to come into compliance by the time your product is ready to be marketed. More important, I think, than the specifics of whether it is a GTP or GMP is really getting back at the whole question of when do you, as an industry, require very pristine standards for the future. I think it is fair to say that, at the present time, there have been several gene therapies using cord blood. However, it has been on fresh cord blood done within 24 hours of birth and no frozen cord blood has ever been examined.

We actually tried to negotiate with the initial studies because this was done on a crash basis that we wanted some assurance that transduction would, in fact, not lead to any adverse consequences when we were told that. Nobody had yet tried to do this on frozen cord blood. This was about two years ago.

That was really kind of a statement of the art of people in the whole area of cord-blood practices. So

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I think a more important thing to consider is if you, at some point in the future, are going to use what you are doing today, you should also think about the future because the consequences could be unknown and, whether or not FDA imposes its specific requirements now or at some time in the future when you are in a 351 or FDNC type of situation, ultimately, the responsibility is yours with the standards and the regulations that we apply to that.

DR. SCRIBNER: Thank you, Dr. Noguchi. We have one last question.

DR. ZOON: One aspect of the question that was not addressed earlier deals with the area of compliance. We see, in this area, two prongs; one is the educational aspect of compliance and the enforcement aspects of compliance.

Our strategy to this date has emphasized, really, the submissions aspects of our framework. But clearly developing a strategy in terms of the compliance aspects is important to the agency. Many of these issues will be presented in either proposed regulations and guidance documents that will have ability for the comment period to be obtained.

As Ms. Pendergast had pointed out in her presentation, at this point in time, we are going to be looking at the accreditation standards and looking for

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those who are accredited. But, clearly, we will be looking in a broader sense at the compliance rate of the industry as a whole in some algorithm that we will have an essence of the level of compliance in this area as well as in the area of those in individuals who do not have participation in such programs.

So, we welcome your comments on this and we appreciate your thoughts in this area and whether you would like to comment now on that or provide comments to the docket, we would be happy to receive them.

DR. SCRIBNER: Thank you, Dr. Zoon.

The hour is late, but we don't want to cut off unnecessary discussion. Are there any further comments or questions for the panel or other people?

Seeing none, I will close this section and defer to Ms. Pendergast for closing remarks.

Closing Remarks

MS. PENDERGAST: Thank you. I would just like to thank everybody for your attentiveness. It has been a long day. We very much appreciate your compliments but, strange as it may seem, we appreciate your criticisms even more because they give us good guidance on what we need to do to strengthen or refine this.

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I think that the robustness of this proposal reflects both our work and also your hard work in your comments and criticisms. So thank you.

Now, today is an Irish national holiday. Before I join my kin and engage in festivities appropriate to the day, I would like to leave you with one small story befitting the day.

A man came into a pub in Dublin and he ordered three glasses of beer. The bartender pulled the three glasses of beer and he went and sat in the corner and he drank the beer, a sip from one, a sip from the second, a sip from the third. And he continued in that vein; a sip from one, a sip from the second, a sip from the third until he had finished all three and then he went back up to the barkeep and he asked for three more.

The barkeep said, "Now, my lad, I don't want to be telling you how you should drink your beer but it gets a little flat. Wouldn't you rather have me draw the beers for you one at a time?"

And the guy said, "That's very sweet of you, but, you know, one of my brothers immigrated to the United States and the other one to Australia and we all pledged that we would always drink beer this way to remind ourselves of the wonderful days we had together drinking beer."

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The barkeep says, "Fair enough, my man." So he goes and he drinks his beer.

The years go by and he is a regular at the pub and he drinks his beer, one beer, second beer, third beer, month after month, year after year. One day, he comes into the pub and he orders two beers. And the bartender pulls the two beers and he sits at his table. And there is a pall over the entire pub. Everyone is somewhat sad. They realized something has gone on.

So when he came back for two more beers, the bartender says, "You know, I just want to say I am very sorry. There must have been a great and serious loss in your family. We would just like to express our condolences. We all feel terribly sorry for your loss."

And the guy looks up at him and he said, "Oh; there is no problem with my family. I have just quit drinking."

Have a wonderful evening.

[Whereupon, at 4:42 p.m., the proceeding were concluded.]