U.S. FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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CELLULAR, TISSUE AND GENE THERAPIES ADVISORY COMMITTEE

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MEETING

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FRIDAY

MARCH 30, 2007

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The meeting convened at 8:00 a.m. at the Hilton Washington DC North/Gaithersburg, 620 Perry Parkway, Gaithersburg, Maryland, James J. Mulé, Ph.D., Chair, presiding.

PRESENT:

JAMES J. MULÉ, Ph.D.	Chair
MATTHEW J. ALLEN, Vet. M.B., Ph.D.	Member
MICHELE P. CALOS, Ph.D.	Member

PRESENT (CONTINUED):

JEFFREY S. CHAMBERLAIN, Ph.D.	Member
RICHARD J. CHAPPELL, Ph.D.	Member
STANTON L. GERSON, M.D.	Member
FARSHID GUILAK, Ph.D.	Member
KURT C. GUNTER, M.D.	Industry Representative
MARY HOROWITZ, M.D.	Temporary Voting Member
JOANNE KURTZBERG, M.D.	Temporary Voting Member
LARRY W. KWAK, M.D., Ph.D.	Member
MARY J. LAUGHLIN, M.D.	Temporary Voting Member
JOHN JEFFREY McCULLOUGH, M.D.	Temporary Voting Member
DONNA M. REGAN, MT (ASCP) SBB	Temporary Voting Member
DORIS A. TAYLOR, Ph.D.	Member
SHARON F. TERRY, M.A.	Consumer Representative
WILLIAM W. TOMFORD, M.D.	Member

PRESENT (CONTINUED):

WALTER J. URBA, M.D., Ph.D.	Member
SAVIO LAU-CHING WOO, Ph.D.	Member

FDA PARTICIPANTS:

GAIL DAPOLITO	Executive Secretary
JESSE L. GOODMAN, M.D., M.P.H.	Director, CBER
ELLEN LAZARUS, M.D.	Captain, USPHS, Medical Officer, Division of Human Tissues, CBER
RUTH SOLOMON, M.D.	
CELIA WITTEN, M.D., Ph.D.	Director, Office of Cellular, Tissue and Gene Therapies

GUEST PRESENTER:

PABLO RUBINSTEIN, M.D.	Director, New York Blood Center, National Cord Blood Program

C O N T E N T S

P R O C E E D I N G S

8:05 a.m.

CHAIR MULÉ: I'd like to welcome you to the 43rd meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee. And today we are focusing on a topic with a very long title. It is Guidance for Industry: Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies.

We will have an FDA presentation and then we'll have a guest speaker, Dr. Rubinstein. And then an open public hearing component followed by questions for the Committee relevant to this topic.

So we can begin by having Gail Dapolito read the conflict of interest statement.

MS. DAPOLITO: Thank you, Dr. Mulé.

Good morning and welcome. I am Gail Dapolito, the Executive Secretary for the Cellular, Tissue, and Gene Therapies Advisory Committee. And before I read the conflict of interest statement, I would just like to request that cell phones and pagers

be silenced. Thank you.

This brief announcement is in addition to the conflict of interest statement read at the beginning of the meeting on March 29 and will be part of the public record for the Cellular, Tissue, and Gene Therapies Advisory Committee Meeting on March 30, 2007.

This announcement addresses conflicts of interest for the discussions of the draft guidance for industry: Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematologic Malignancies and for a discussion of scientific issues regarding minimally manipulated, unrelated, allogeneic, peripheral blood stem cells.

For the discussion of topic two on the draft guidance for industry, Drs. James Mulé, Mary Horowitz, and Mary Laughlin each received a waiver under 18 USC Section 208(b)(3). A copy of the written waiver may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12830 of the Parklawn Building.

Dr. Kurt Gunter serves as the Industry Representative acting on behalf of all related industry and is employed by Hospira, Inc. Industry representatives are not special government employees and do not vote.

With regard to FDA's guest speaker, Dr. Pablo Rubinstein, the Agency has determined that the information provided by him is essential. The following information is being made public to allow the audience to objectively evaluate any presentation and/or comments made by him. Dr. Pablo Rubinstein is employed by the National Cord Blood Program at the New York Blood Center.

This conflict of interest statement will be available for review at the registration table. We would like to remind participants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants needs to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Committee of any financial relationships that you may have with any firms that could be effected by the Committee discussions.

Thank you.

Dr. Mulé?

CHAIR MULÉ: Thank you, Gail.

We'll go around that table and introduce the Committee members. On my left.

MEMBER WOO: Savio Woo from the Mt. Sinai School of Medicine.

MEMBER LAUGHLIN: Mary Laughlin, Case Western Reserve University.

MEMBER HOROWITZ: Mary Horowitz from the Center for International Blood and Marrow Transplant Research at the Medical College of Wisconsin.

MEMBER TOMFORD: Bill Tomford, Massachusetts General Hospital.

MEMBER GUILAK: Farshid Guilak, Duke University Medical Center.

DR. GUNTER: Kurt Gunter from Hospira. I'm the Industry Rep.

MEMBER REGAN: Donna Regan from the St. Louis Cord Blood Bank at Cardinal Glennon Children's Hospital.

DR. LAZARUS: Ellen Lazarus, Medical Officer in Division of Human Tissues in the Office of Cell, Tissue, and Gene Therapies.

DR. WITTEN: Celia Witten, Office Director of the Office of Cell, Tissue, and Gene Therapy at the Center for Biologics at FDA.

MEMBER McCULLOUGH: Jeff McCullough from the University of Minnesota.

MEMBER CHAMBERLAIN: Jeff Chamberlain from the University of Washington.

MEMBER KWAK: Larry Kwak from M. D. Anderson Cancer Center.

MEMBER CALOS: Michéle Calos from Stanford University.

MEMBER ALLEN: Matthew Allen from State University of New York, Syracuse.

MEMBER CHAPPELL: Rick Chappell, University of Wisconsin.

MEMBER URBA: Walter Urba, Portland,

Oregon.

MEMBER GERSON: Stan Gerson, Case Western Reserve University and the Case Comprehensive Cancer Center.

MEMBER KURTZBERG: Joanne Kurtzberg, Duke University Medical Center.

MS. TERRY: Sharon Terry, Genetic Alliance. I'm the Consumer Rep.

MEMBER TAYLOR: Doris Taylor, University of Minnesota.

MS. DAPOLITO: Gail Dapolito, Executive Secretary.

And I'd like to introduce Rosanna Harvey, the Committee Management Specialist for the Committee.

Thank you.

CHAIR MULÉ: Jim Mulé, H. Lee Moffitt Comprehensive Cancer Center, Tampa.

MS. DAPOLITO: And we have the pleasure of honoring one of our distinguished members this morning. And I'd like to ask Dr. Goodman to come up please.

DR. GOODMAN: Well, good morning. And I

just have the tremendous and brief pleasure of building on the opportunity of actually being able to be here for all of yesterday and today to honor Dr. Mulé.

Jim has been, I guess, on our Advisory Committee I think for four years. Is that correct? Okay, that's a long -- a lot of service. And also as the Chair for the last year. And I just know from all of the staff, you know, what a tremendous job he's done, what expertise he's brought to this.

And I think that yesterday's meeting, in a way, and today's as well, are examples of just how incredibly important what he has done and also I'll take this opportunity to thank the other people serving here today on the Committee who are working with Jim.

What we do is so important. It's not just important to the scientific community. I think we saw yesterday how difficult the decisions are, how complex, and how they effect people, patients, physicians, et cetera.

So the other thing that I think is a very

exciting part of what has gone on in the last three or four years and I keep telling people about the area of therapies that this Committee works on is -- we're talking not just about products but about whole fields, we're talking about discovery, we're talking about the development of things with the incredible potential to prevent and cure disease that is so different from so many of the other therapeutics.

And that's where Jim's expertise in immunotherapy, tumor immunology, his work in helping bring along some of the cell therapies has been so important. So, again, what he's done -- and not just being here, it's not just what we're doing, it's also what you have brought to it.

Without the Committee's work and the Chair's work -- and we absolutely depend on this because we can't have this breadth of expertise and knowledge and also the decisions and the information is so complex that the discussions here really do inform us.

And, you know, I can say in the last couple of years every time I've heard about a Cell and

Gene Therapy Advisory Committee and how it went from the staff, if I haven't been there, I've heard about well, gee, we learned a lot. We got a lot out of that.

So we really owe a huge debt to you for your service and we will continue to nag you and ask you for help I am most certain. So thank you very much.

(Applause.)

DR. GOODMAN: Okay. So this says that this Advisory Committee Service Award is presented to Dr. James J. Mulé in recognition of distinguished service -- and this is key -- to the people of the United States of America. So thank you so much.

(Applause.)

CHAIR MULÉ: Well, it's been an honor for me to be able to serve the FDA in this capacity for the past four years. It has also been a great delight for me to meet so many wonderful people and so many well-read experts in the field. And I look forward to coming back on occasion.

And also I'd like to thank Gail and

Rosanna for really helping put this all together for us.

Okay. So we'll start with the FDA presentation. And it is an overview draft guidance for industry: Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematologic Malignancy.

Dr. Lazarus.

DR. LAZARUS: Well, good morning. And it is such a great honor and such a great pleasure for me to welcome all of you, to thank Dr. Mulé, the members of the Committee, the audience, my colleagues at CBER for being here and for lending your expertise and your careful consideration of this topic.

I won't repeat the title of the guidance. It's long for a reason. Every word has meaning. And what I'm going to do is give you an overview of this draft guidance.

And I'm going to skim over some of the topics and I'm going to dig deeper where there are issues that we feel would benefit from discussion by

the Committee.

I'll give you a background, a very brief background of the regulatory framework and a little bit of a history of the development of this draft guidance. I'll explain the purpose and the scope of the guidance and walk you very briefly through the proposed license application procedure.

I'll spend a little more time and give you a little more detail about the chemistry, manufacturing, and controls or CMC section of the draft guidance and also very briefly summarize the establishment description section.

And then I'll devote a little bit of time to the applicable regulatory requirements for these products and then finally I'll describe the part of the guidance that explains the post-marketing activities that the license holders would engage in.

And then at the end, I'll share with you our plans for how to proceed with the guidance and some other related issues.

So first I'll explain briefly a history of the promulgation of the regulations for human cells

tissues and cellular- and tissue-based products or HCT/Ps. As you all know, in the mid to late 90s, FDA proposed a risk-based, tiered regulatory framework for regulation so these products.

And this was implemented by promulgating three final rules, namely the registration and listing final rule, the donor eligibility rule, and Current Good Tissue Practices. Those rules were implemented on May 25th, 2005.

Now under this framework, it is established that cells that rely on metabolic activity are regulated also as biologic products and they are subject to IND and BLA requirements.

So subsequent to publication of that regulatory framework, in 1998 we published a notice in the Federal Register that had another very long title but it started with request for proposed standards for unrelated allogeneic placental umbilical cord blood and peripheral blood, hematopoietic stem progenitor cells.

And in that notice, we explained how after a series of public meetings we had come to the

conclusion that it might be possible to develop product standards and establishment and processing controls for these products that would relate to clinical data submitted to a public docket.

So we requested submission of comments about this, including establishment controls, CMC, and product standards for both the minimally manipulated, allogeneic, unrelated donor cord blood and peripheral blood stem cells.

So after the comment period was closed and several series of discussions, and analyses of the data in the docket, we held an Advisory Committee meeting. At that time it was called the Biologic Response Modifiers Advisory Committee to discuss clinical transplant outcome data for cord blood.

And many of you here today were at that meeting. And it was very fruitful, very helpful to us. And the Committee discussed safety and efficacy issues that FDA should take into consideration.

So subsequent to that meeting, the CBER Task Force determined that, indeed, there were data submitted to the docket and available in the published

literature that were sufficient to permit development of recommendations for applying for licensure for cord blood.

And consequently we published the draft guidance that is under discussion today.

So like all draft guidance, this is open for public comment. As you know, the comment period ends very soon, in April. And like all guidance, it represents FDA's current thinking and does not establish legally enforceable responsibilities.

So the guidance uses language that indicates that these are recommendations except where, throughout the guidance, there are specific regulatory or statutory requirements cited. And as is the case with other guidance, an alternative approach could be used.

So the stated purpose of the guidance is basically to help the industry understand how to apply for licensure for cord blood products for specified indications that I'll discuss in a minute. And the guidance explains the applicable regulations in the Code of Federal Regulations for these products.

And we meant that this guidance would be very helpful to people because the applicable regulations, as I described, involve both the human cell and tissue rules as well as biologics regulations and GMPs. And then finally it provides information about manufacturing cord blood and how to comply with the applicable regulatory requirements.

It is important to know what cord blood products are covered under this proposal. Basically, it is addressing the cord blood that is minimally manipulated and that is intended to be used in recipients unrelated to the donor.

Equally important is knowing what it doesn't cover, which are the peripheral blood stem progenitor cells that are minimally manipulated and from unrelated allogeneic donors. And it doesn't apply to other cord blood products. For example, those that are minimally manipulated or those that are for indications other than the one described in the guidance.

Finally, it doesn't apply to cord blood for autologous or family-related use, although in the

guidance there is a statement that we encourage the private banks to follow these recommendations where they are relevant to those establishments.

So now is a good time for me to discuss in a little more detail one of the issues that we feel is important for consideration by the Committee and that is the clinical indication that is specified in the draft guidance. So, as you know, the indication is in that long title: for hematopoietic reconstitution in patients with hematologic malignancies.

Now the 1998 Federal Register notice described some definitions for hematopoietic reconstitution as evidenced by neutrophil and platelet recovery in order for us to be able to evaluate data from disparate sources. We received a lot of information on those outcomes as well as other transplant outcomes.

And the preponderance of those data were describing outcomes in patients with hematologic malignancies. In fact, up to 70 percent of the recipients of cord blood that were described in the data submitted to the docket has hematologic

malignancies.

There was a very long list of other indications in the data submitted to the docket but there were much fewer data for each of those other indications. For example, for patients with all genetic diseases, that group comprised 25 percent and there were smaller numbers of transplants in patients with other diseases including bone marrow failure conditions.

So the question that we will look forward to discussing with the Committee is what data might be needed to support other indications. And generally we would require data demonstrating the safety and efficacy of the product for transplantation in patients with other diseases.

For example, engraftment data, survival, measures of mitigation of the defect, for example, immune reconstitution or an increase in the level of deficient metabolic enzyme or a correction of hemoglobinopathy. And, in general, any other marker of clinical benefit. So I'm sure that we will have a very interesting discussion on this topic.

So walking through the guidance, the next section describes how the manufacturer could use it to apply for a biologics license in a manner that we felt would be a streamlined approach to licensure. Essentially the applicant would demonstrate in their application that they have followed the guidance recommendations by submitting data that I will describe.

We make the point in the guidance that the manufacturer can modify any procedure in the guidance. And in that case, they would be expected to provide evidence demonstrating that their modification will provide similar assurances of safety, purity, potency, and effectiveness of their cord blood.

So this guidance provides specific recommendations if the manufacturer wishes to rely on the data in the docket. And under this construct, the biologics license would apply to cord blood manufactured at the time of and subsequent to approval of the license application.

The cord blood manufacturer does not have to follow this guidance when applying for a license.

However, if not, they would be expected to submit a BLA for their cord blood containing data from their own non-clinical laboratory and clinical studies demonstrating that the product meets the requirements for safety, purity, and potency described in the Code of Federal Regulations.

And if that were decided to be the way that a particular manufacturer would want to go, we would recommend consultation about the alternative approach before submission of the license application.

Let me walk you briefly through the proposed license application procedure. First, like any BLA, there is a form, Form FDA 356h, Application to Market a New Drug, Biologic or Antibiotic Drug for Human Use. It is submitted to the Document Control Center. And the guidance describes, we hope, comprehensively the information that should be included. And it also explains what FDA will do with that information.

So I'll summarize that here. You can read this slide. I'll just point out that the guidance explains that in addition to the information listed on

this slide, the manufacturer would include a statement that they were citing to the data in the docket. And the manufacturer would indicate that they are ready for inspection.

When FDA gets the application, we would review it. We would schedule a pre-license inspection as soon as possible after receiving a complete application. If, however, the application is determined to not be complete, we intend to identify and advise the establishment of the additional information that would be needed to be submitted to complete the application.

Okay, now I'm going to briefly discuss the -- I'll summarize the information in the section entitled Chemistry Manufacturing and Controls. And, like I said earlier, I'm going to dig a little bit deeper when I get to parts of the CMC that we have targeted for Committee discussion.

So the first part of this section has a table. And the table gives the product description and characterization. Specifically, it lists the required and the recommended tests and results that

were used to manufacture the cord blood that resulted in the submission of data to the docket.

The first part of the table describes the safety testing. And the infectious disease testing, as I'm sure most of you are aware, is required testing in accordance with the donor eligibility rule where a sample of maternal blood is required for testing for the so-called relevant communicable disease agents and diseases.

Also required in the CFR is sterility testing. And in the guidance, we recommend that the testing for bacteria and fungi be done on a sample from the collected cord blood prior to any further processing and also on a precryopreservation sample.

Then finally, a recommended safety test if hemoglobin assay using a cord blood sample just to exclude a product from a donor with a homozygous hemoglobinopathy.

The second set of tests are those for purity and potency, which we recommend as three analytic assays that are performed using a precryopreservation sample. First is total nucleated

cells and that number five times ten to the eighth TNC per cord blood -- times ten to the eighth per cord blood unit is based on a hypothetical 20 kilogram recipient who receives a total nucleated cell dose of 2.5 times ten to the seventh per kilogram but assuming 70 percent post-stall recovery so that the administered minimum dose would be 1.7 times ten to the seventh per kilogram.

The viable nucleated cell percentage of greater than or equal to 85 is, again, derived from data in the docket. And the viable CD34 cell count of greater than or equal to 1.25 million per cord blood unit is based on a minimal concentration of CD34+ cells of .25 percent prior to cryopreservation.

And then the last section of the table describes what we recommend for identity testing for the cord blood, specifically HLA typing from a cord blood sample, confirmatory HLA typing using an attached segment to assure the relationship between the confirmatory type and the cord blood. And then finally ABO/Rh testing using a cord blood sample.

So the next part of the CMC

recommendations is the manufacturer information. And basically we require identification not only of the applicant, of course, but also for the other establishments that are performing manufacturing steps under contract agreement or other arrangement with the applicant. And those would include, for example, the cord blood collection sites and the laboratories performing donor testing for relevant communicable diseases and also for product sterility.

The manufacturer information section also should include the precautions taken to prevent contamination and cross contamination. And I'm just going to point out a few that are unique to cord blood including the avoidance of simultaneous manipulation of more than one cord blood product in a single area. And also the precautions that are taken to prevent contamination and cross contamination by equipment used to process the product.

The narrative description of the manufacturing area covers all the areas involved in collection, volume reduction, packaging, labeling, cryopreservation, storage, and shipping of the

product.

The CMC section then, of course, includes the methods of manufacturing. And we submitted a list of those SOPs that describe critical processes that we feel should be submitted with a license application. And I'll just point out a few that I think are of particular interest or maybe need some clarification.

One is the selection SOPs. And what we are thinking of here is that we would like to see the procedures in place to describe how the cord blood is managing the data relating to inventory or communication or registration of their inventory, the procedures for handling search requests, and any procedures that the cord bank has in order to handle donor matching and selection for the cord blood product.

Also for shipping and handling procedures, we would like to see the procedures that the manufacturer has in place for shipping the product to the transplant centers which, as we know, are all over the world. We would like to see the procedures that are recommended by the cord blood manufacturer for

thawing and preparing their products for administration. And we would like to see the procedures that the manufacturer recommends for emergency product recovery in the event of failure of a container or tubing that could result in, you know, difficulty in infusing the product to the patient.

For the validation data summary, we have recommended in the guidance that data be submitted from three consecutive separate cord blood products.

The methods of manufacturing also include flow charts showing a visual representation of the manufacturing process controls, including information on transfers and where in manufacturing those are performed.

And also of particular interest, I think, is the section of the guidance that describes control of aseptic manipulations, which would include a description of the process parameters that are monitored and the procedures that are used to monitor sterility and the conditions and the time limits for each processing step.

Other important CMC information that would

be required is a description of the container closure system. And we have explained in the guidance that the applicant could reference an NDA or 510(k) or master file for the containers. And we have stated that the manufacturer should provide evidence of container and closure integrity for the duration of the proposed storage period.

Finally, other CMC information that would be submitted would be methods validation or verification, as appropriate, for infectious disease testing. Under the donor eligibility rule, the manufacturer would be required to use kits that are licensed, approved, or cleared for donor eligibility determinations. And other tests that are performed would also be explained in this section of the CMC in the license application.

The labeling I'll discuss more. There's a section in the guidance 7(b)(2) that describes the labeling information that would be submitted.

Okay, so now this is the right time for me to discuss the issue that I touched on earlier. What products would the license apply to? We know,

obviously, for cord blood this is a very important issue because of the thousands of products that are already in inventory.

And we know this is going to be the subject of very interesting discussion and consideration by the Committee. So let me touch on now the information in the guidance that addresses cord blood that have been previously manufactured.

First, the cord blood that has been previously manufactured using the same procedures could be handled in a manner described in the guidance, namely, that the license would apply to those cord blood products that were previously manufactured in accordance with the information provided in the license application where documentation is provided to demonstrate their comparability to the cord blood that is currently being manufactured.

Also covered in the guidance is the cord blood that has been previously manufactured using different procedures. As we know, the technology for processing cord blood has evolved over time and, of

course, any change has the potential to effect the safety and the quality of the cord blood products.

However, we know that transplants are being performed using products that have been inventoried for years. And they are very successful.

So what we would expect the manufacturer to include in their BLA would be a demonstration of comparability of the previously manufactured cord blood products to the currently manufactured product similar to what I just said. And the manufacturer would provide evidence that the methods, the facilities, and the controls that were used to manufacture those products conformed to GMPs and to the other applicable regulatory requirements.

So we've recommended an approach for demonstration of comparability that would entail submission of separate validation summaries for those cord blood products including data on the product characteristics such as total nucleated cell count, viable CD34 cell content, and colony-forming unit assays, for an example.

Alternative methods could be used and also

possibly helpful would be clinical outcome data obtained from those previous iterations of the manufacturing process where the particular manufacturer has those data. And then finally citation to medical literature could be helpful in this regard as well.

So as I said, we recommended certain assays that might be used to explain the product characteristics and could be used to determine comparability because these markers have been shown to correlate with the clinical outcome of engraftment. For example, an increase in total nucleated cells is associated with shortened time to engraftment and the CD34+ cell dose has been reported as being associated with the incidence and the speed of neutrophil recovery.

And then finally a correlation between two of these or all of the three markers have been reported, including correlation between CD34 number and colony-forming units as demonstrated by several researchers, including Dr. Cairo in a couple of his publications. This table is taken from an abstract

that was published in 2004 that shows a nice linear correlation between colony-forming units on the Y axis and CD34+ cell content on the X axis.

So as part of this consideration of comparability we, again, special for cord blood, have to address the issue of the types of samples that are available to do the comparability studies. So first would be the segment, which would be the cell sample attached -- integrally attached to the cord blood product container, which has some clear advantages. It is exposed to -- the material in that segment is exposed to the same processing, freezing and storage conditions as the product itself. And there is a low or a nonexistent risk of mislabeling between the segment and the cord blood product.

The obvious disadvantage, of course, is the limitation on the amount of sample in a little segment for testing. And a finite number of segments that are actually attached to a particular product.

So another option is using the cryovial samples which are processed similarly as the cord blood product but are separate, non-attached aliquots.

The advantage being that an increased number of aliquots may be stored and retrieval of the sample for testing doesn't effect the cord blood. For example, it wouldn't necessitate removal of the cord blood from liquid nitrogen and exposure to ambient air temperatures.

The disadvantage, of course, is that the sample may or may not be representative of the cord blood product. It may be exposed to different freezing and storage conditions. And there is, of course, the increased risk of mislabeling between the cryovial and the cord blood product.

So finally, perhaps the gold standard material for comparability testing, would be the cord blood unit itself. It is, of course, the most representative of the product actually received by patients and it is sufficient in size to obtain as many samples as necessary for testing. Obviously products used for comparability studies can't be used for transplant.

So we look forward to a very interesting discussion on the comparability issue.

And now I'll march over to the next section of the guidance which is the establishment description section which we hope will be helpful for the cord blood manufacturers in providing the information we need in this section of the BLA.

The section describes the general information required, including a floor diagram showing the location of the major equipment, a description of the processing areas, a description of the manufacturing activities that are taking place in adjacent areas, and the flows for the product, the personnel, equipment, and waste.

I'll just point out a few of the topics in the specific systems for the establishment description including submission of information about the facility controls that would include their environmental monitoring program.

And also there is fairly detailed information in the guidance on computer systems information that we would like to see in the application, including information and validation summaries for the computer systems that control

critical manufacturing processes. And the guidance includes several examples of such systems.

Also in this section would be contamination and cross-contamination information that supplements the information submitted in the CMC section. Here, more specifically, would be the equipment cleaning procedures and the containment features; for example, air handling and procedures that are used for decontamination and equipment cleaning when there is a breach in container integrity which, as we all know, is an occasional problem with cord blood processing.

Okay, so now I've described the license application procedure, the chemistry manufacturing controls and establishment description. And now I'm going to describe what we hope will be a particularly helpful part of this guidance, because it describes the applicable regulations and post-marketing activities. And we've done an extensive evaluation of all the different regulations and put citations to those regulations in one section of the guidance that we hope the manufacturer will find to be a helpful

reference.

The applicable regulatory requirements are listed on this slide. And I won't read them all but they comprise biologics products, GMPs, labeling and advertising regulations, as well as the regulations promulgated in 21 CFR Part 1271 for HCT/Ps, including, as I said, the three rules.

And I'll just point out that for the Current Good Tissue Practice, we've said that, where there is a conflict between the GMPs and the GTPs, the more specific regulations supercede the more general.

And we've also said that compliance with the GMPs would generally result in compliance with the applicable GTPs although there are some exceptions, namely the GTPs that are not covered under the GMPs include, among others, the donor eligibility requirements, the provisions specific to spread of communicable disease, the manufacturing arrangements, and the provisions for requesting exemptions and alternatives.

The next couple of slides list the applicable GMPs. You can read these. I'll just point

out for particular interest for a cord blood manufacturer would be packaging and labeling control regulations in the GMPs. And this would include physical separation from other operations and expiration dating determined by the stability testing program which is an interesting issue and perhaps that will be something that will be discussed today, and shipping containers and conditions to be maintained during transit. Again, cord blood products being shipped all over the world and needing to be maintained in a manner to retain their viability is a very critical issue.

The GMPs include label and labeling content, including regulations for prescription drug labeling, for package labeling, and there are provisions for partial labels, and then finally, the bar code label requirements that are applicable to cord blood.

Finally, the GMPs include such issues as holding and distribution. You can read this list. And of interest also would be regulations regarding returned and salvaged products.

Okay, so that's pretty much the first four-fifths of the draft guidance. At the end, we've described the post-marketing activities that we think the applicant would be engaging in, including some that are required.

First a recommendation that there be a collection of clinical outcome data from the transplant centers. And we recommend that the cord blood manufacturer analyze the clinical data as a quality indicator for their products. And we've recommended that the manufacturer should evaluate the data with an eye to determining whether any adverse experiences or other unexpected outcomes may be due to manufacturing problems.

Now there are also required post-marketing activities and the guidance lists those, including the changes to be reported, the regulations for adverse experience reporting, and the regulations for biologic product deviation reporting.

So that's it for the guidance. Now what I'm going to do briefly is explain to you what we think are the next steps. We've published the draft

guidance. We are having this meeting. And we know that you will all give us some very thoughtful input on all of these topics. And we intend to carefully consider all of your recommendations and also, we'll be very interested to hear the comments from the other attendees.

We will review and address, of course, the comments that have been submitted to the docket. And using all this information, we will finalize the guidance. And we intend to include in the final guidance the date for implementation of the IND and BLA requirements that would end this period of delayed implementation for cord blood.

Now as has been the case up until now and will continue, the license applications for cord blood could be accepted at any time.

Now also a related topic that we are looking forward to discussing today is the regulatory issues and data for the unrelated allogeneic peripheral blood stem cells. So as most of you know, these products were also the subject of the 1998 Federal Register notice and at the time that the

comment period was closed, we hadn't yet received data for the unrelated donor PBSCs although we had, of course, received extensive data for cord blood.

But once we addressed the issue for cord blood, our attention naturally turns to these products. And we've come up with a list of some considerations that we think are of particular importance for thinking about unrelated allogeneic PBSCs, including issues such as the requirement or -- HBCs actually only require often limited manufacturing beyond the donor selection and eligibility determination and recovery of the product, testing, labeling, and distribution of the product.

Also, a consideration is that several post-recovery manufacturing steps are performed in a laboratory at the transplant center. And also most of these products are manufactured by establishments that are participating in the NMDP registry.

And other issues that are very special for PBSCs include donor mobilization, cell selection depletion, which is commonly performed on these products, and donor lymphocytes which are often

obtained from the same donor as the PBSC product or even might be derived from an aliquot of the product itself.

So that's just, I think, probably a partial list of some of the issues that would be important for our consideration for the PBSCs.

Thank you all so much for your attention. We look forward to a very interesting discussion. I believe I have just a few minutes to address questions that the Committee might have about the guidance.

CHAIR MULÉ: Thanks, Dr. Lazarus.

Questions? Again, we'll have a series of four questions at the end of this session related to this, specific topics for the benefit of the FDA. So if there are no other questions, we'll go ahead to Dr. Rubinstein's presentation.

DR. RUBINSTEIN: Good morning. I was a little surprised and very grateful for the invitation to address this panel today. And it occurred to me that the annunciation of the guidance for licensing in a way logically ends the development of cord blood to a point at which it can be regulated in this manner.

The story that I have for you is a little dispersed, in a way, because it will review the developments within the period of beginnings which now are 14 years long. And the guidance that we just heard so beautifully explained has taken us really to complete a part of the cycle in which we went from zero on the regulatory end of things to a complete guidance document. We now know how to do these things.

The evolution during this period has been gigantic and has been remarkable. Within this period we have learned about GTPs and we have implemented all kinds of controls and methods for gathering information and preventing problems, making sure that the cord blood manufacture and cord blood procedures in issuing, et cetera, are all up to par and, in some cases, actually ahead of comparable procedures with other stem cell sources.

There have been technical advances during this period, now led to the existence in the market of equipment that provides a completely closed control of the manufacturer of a stem cell product from cord

blood and perhaps from other sources. There have been remarkable improvements in the application of IT to selection search for optimally-matched cord blood.

There has been legislation because the expense of preparing cord blood, as you undoubtedly are quite familiar, is very, very onerous. And it has been felt that the banking part of this -- I hate to call it industry but I guess that is what it is -- the banking industry have been found to require external sources of help, hopefully for a limited period of time, but it is essential.

And finally I think it has demonstrated clinical usefulness and there are currently in excess of 10,000 unrelated cord blood transplants that have been performed.

From our own bank, there have been over 2,300 patients who received transplants from us around the world. Some of these patients, one can be completely certain, would not have received stem cell graft had it not been for the existence of cord blood.

There are numerous countries in which the attempt at organizing a donor registry with adult

donors have failed to result in a single transplant.

One of the remarkable aspects has been, although, of course, you cannot see these, in the last maybe five or six years, there has been a very fast development of cord blood utilization in Saudi Arabia. And it is a hopeful sign that more than 50 percent -- this is really now hovering about 65 percent of the grafts going to Saudi Arabia from our bank have been donated by Jewish families.

One wonders about the consequences of revealing that fact but the effects have been just as good as if the recipients have been of the same religion.

Of these transplants, and I use our data only as an indication to you of what you can expect to see from the overall data around the world, the single cord blood unit as a transplant is now joined by multiple cord blood unit techniques. These methods of multiple transplants simultaneously have been pioneered by the Minnesota group who developed the method in a way similar to development of bone marrow transplantation where initially the transplants failed

because they didn't have enough cells. And that led to the replacement of the sternum as a site for collection, for the hips.

The data that I will show you, which is really very limited to aspects that can be of major importance for the work of this Committee, we were limited to the single cord blood unit transplants, although, as you can see in a few years, we are now up to ten percent or more of multiple transplants.

There has been a change, a rapid change in the number of transplants per year that we have been able to provide. And the only thing I would like for you to look, is the dramatic falling, the number of our submissions of grafts in the period of 2000 to 2002.

During this period, there was a dramatic expansion around the world of the available inventory of cord blood. And consequently, it was a classical competition that drove us to about a half of the transplants we used to prepare.

And there has been a subsequent resurgence which is representative, I think, of the overall

experience in cord blood banking where the last years have witnessed an enormous expansion of the interest in cord blood and the utilization of it.

Single transplants are now being increasingly challenged by multiple transplants, even for children. And our last year has shown a slight decrease in the number of single transplants with a vast increase, on a percent basis, of the multiple ones.

One of the important things in our experience is that we have follow-up data for most of these transplants, for at least a year. And in most cases of survivors, for the life of the patient since the transplant.

There are some transplant centers that are recalcitrant with respect to some patients. And one of the reasons why cord blood has been so well received can be gleaned from this slide. There is a patient and the cord blood unit and these are identical.

Now if you examine these, and this is a very modern typing for cord blood, we only have to

deal with three loci, A, B, and DR. And in bone marrow we now know quite well that HLA-C is an important locus that determines survival of the transplant and helps survival of the patient.

For cord blood, even though the numbers of transplants are now in excess of 2,000, we still don't see evidence that HLA-C is important. There may be a trend but -- and I hope that very soon we shall be able to understand and identify the reasons for this difference.

Another interesting, perhaps paradoxical thing, is that A and B don't have to be tested at very high resolution. We have retrospectively updated the resolution of all the transplants that have been done and we still don't see statistical evidence for the importance or the improvements that are possible if A and B are also used at high resolution.

But all of these, of course, require numbers. And numbers are difficult to manage when you are dealing with transplants that are mostly mismatched.

On the other hand, there is very good

evidence that DRB1 must be used at high resolution. The significance of the typing if you use DRB1 at low resolution, it is diffused and it does not reach significance even in our data. So DRB1 is an important high-resolution locus for us. But the lack of necessity to match at high resolution for A and B makes it far easier to encounter optimal matches using cord blood.

And I will show you some of the data that we have gathered, most of the comparisons have been done or all the comparisons have been done, in fact, in cooperation with IBMTR, a cooperation for which we are extremely happy and very grateful.

In this talk, I will just use a few indices for outcome endpoint. So engraftment and transplant-related mortality, overall survival, and comparison with bone marrow in some cases will be methods for showing you what cord blood is doing today.

And all the patients, as I said before, are the recipients of a single cord blood unit transplant. And the last ones are in December of 2005

to allow for follow up. We have 1,779 patients that fit this description and they -- 91 percent of them or 1,600 have follow-up data.

The major categories are for everyone's experience, hematologic malignancies, genetic diseases however are now 413 cases, severe aplastic anemia 48 as a representative of marrow failure syndrome. And neuroblastoma and a few other conditions account for the rest.

Within the hematologic malignancy, there are no surprises. The data are very much in agreement with expectations. And I apologize for this. This is a result of a different version of Windows that PowerPoint will not show the lines. The slides were made in a earlier version, and some of the new versions will pick it up, but not all. So you will see just the crosses at the point where patients have been censored.

So for leukemia and other conditions, the engraftment profile is very similar. There is no significant difference. The transplant-related mortality shows exactly the same thing. Leukemia and

other malignancies evolve exactly the same way. And finally, overall survival is very similar in all of these malignancies.

These homogeneities are interesting because it, in a way, was at least unexpected by us. We had hoped to see some differences. All the differences, however, are accounted for almost exclusively by the state of disease at the time of transplantation.

The data that I will show you here are just a few abstracts from data that were published by Mary Eapen from IBMTR. And these slides come from her presentation at ASH. It is very hard to see. I apologize for that.

But if you persist, you will see a white line that is bone marrow transplantation fully matched patients, and that engrafts faster than the cord blood -- either matched or mismatched. And there are differences in cord blood from matched transplants and mismatched transplants.

So for engraftment, bone marrow is faster and more complete. A higher percentage of patients

will get their grafts accepted initially with bone marrow. But the leukemia-free survival in U.S. children is longer and better when cord blood is matched. The numbers, however, are small. And more numbers are necessary before this information becomes fully acceptable.

But it is quite clear, and it is being confirmed subsequently, that under fully-matched conditions, meaning A and B at load of solution, cord blood can provide certainly at least as good, and very likely a better, leukemia-free survival, at least in children.

In adults, these three curves compare bone marrow, that's in black, fully matched, bone marrow with one mismatch, that's the point line at the bottom, and cord blood with one or two antigen mismatched in the middle. The differences were not significant. This is a study by Mary Laughlin, also with IBMTR, and our group.

Now of relevance to this guidance document that we are so excited about and for which, I think, we -- certainly we are most grateful to FDA -- it is

a high point, I think, in their development of regulatory oversight for this area, oversight that is another source of pride to all of us in the U.S. I think FDA has been remarkably discreet and prudent, and has taken their time. And they have done their work, and have come up with something of tremendous value to us.

So one of the issues that I have with this guidance, and it is the limitation of the indication to a single category of diagnosis. The philosophical reasons for my discrepancy with that decision are that the cord blood is supposed to reconstitute the patient, hematologically and immunologically.

There are so many clinical components to other aspects of the recovery of these patients that it is a little unrealistic to expect that a source of stem cells can have a profound effect on those clinical aspects.

Just to give one -- the degree of advance of a disease cannot be in any way affected by the cord blood versus bone marrow controversy anyway. Bone marrow is also not licensed. So we cannot blame them

for lack of consistency.

But in any event, in this slide I give you also the numbers of these transplants that were reported to the original docket. As a guidance to tell how much more security we have in the numbers, all of the trends that were discernible with the earlier data have been now confirmed, every single one of them.

And in these slides that follow, I will show you a comparison with genetic diseases that are, unfortunately, the line is missing, but you can follow the top line of points. Those are patients with genetic disease, and this is engraftment.

The difference between them and hematologic patients with hematologic malignancies is very substantial. It is highly significant. And it certainly is not any less effective in these conditions from the point of view of hematological reconstitution.

On the other hand, the curve of patients with severe aplastic anemia is lower. And no surprise from the clinical point of view. But it is nice to

see it confirmed. And, again, the difference is highly significant.

In this one, we have the transplant-related mortality. And, again, there is an improvement of the probability of escaping a transplant -- a mortality from transplant-related causes for patients with genetic disease. And this is highly significant.

Here, severe aplastic anemia patients didn't do as well upon entry from the curve, but the difference is not significant. And this is most likely because of the small numbers of patients, particularly small numbers in the right side of those curves.

And the overall survival is also highly significantly better for the patients with genetic disease. One might say there is no surprise here, but then this opens the question, why should indications for genetic diseases that are helped by the replacement of stem cells, why should they not be included among the indications for licensed product?

Now this is, will become not

understandable without the lines, but this slide shows that most of the genetic diseases describe one pattern of overall survival, with 12-month survivals in the order of 60 to 80 percent. The exception is bone marrow failure syndromes, where the survival goes down to about 40 percent.

Now I will just give you an idea of the numbers of patients that are included in these diagrams. Rapidly, for immune deficiency diseases, mostly patients with SCID, we have studied a total of 124 patients. Bone marrow failure disease is Fanconi, osteoprotosis, Diamond-Blackfin, and others, 121 metabolic diseases, including Hurler, and related diagnosis, adrenal leukodystrophy, Krabbé and others is 111.

Thalassemia and sickle cell disease, there are a few patients, 18 and seven respectively. But in these two conditions, it is perhaps where it is most evident when you get engraftment, you get a cured patient.

So a few thoughts about selection of units. Again, my apologies for the lack of lines.

What you see here are the effect of mismatches on transplant-related mortality. On the left the data are plotted by the presence or absence of HLA-mismatched transplantation. At the bottom, you see some points with a zero, there are a few of them, and those are patients where the donor is exactly identical to the recipient based on the HLA criteria that I described earlier.

Then there is a line for one mismatch, and over that is a line for two mismatches, and then one for three. Taking the number one, the line for one mismatch as a reference point so that we don't bias by taking one extreme or another, these patients are significantly different from those that have complete matches. They are also highly significantly different with patients that have received transplants with two.

In transplants with three, which should be more significant because they seem more different, in fact are not significant strictly, and they are near the threshold of significance.

On the right side we see the classically accepted variable of the cell dose and, again, there

is a stepwise progression from higher cell doses to lower cell doses, increasing transplant related mortality likelihood.

So we have attempted to combine these two variables. There are a number of statistical signs that the two can compensate for one another, and that together they condition a better approach. And it is correct.

And so we can define the survivor that I should have been able to show you and couldn't because of the lines, the absence of lines, but in the gist of this data is that, when you combine a good cell dose with a poor match, you can get better results. And when you have a low cell dose only, then you should have a better match.

The main threshold for the cell number is about 2.5 times ten to the seven. Above that, this is TNC, above that number, patients seem to be doing quite well. Below that number, there is a precipitous decrease of the survival in two antigen mismatched transplants. This is shown in these lines here, or should have been shown by the lines here.

The pointed lines are two mismatches, and you have a red one. Those are two antigen mismatches. Well, it is very hard to see, so I will not tax you. And unfortunately, the message here is completely lost.

However, the survival is again conditioned by these two variables, and they are working together. One mismatch in an intermediate cell dose range between 2.5 and fives times ten to the seventh behaves very well. Whereas below, clearly a different survival.

Now this is a beautiful slide normally with two curves. And here you only see the points. This compares adults with a TNC level of under 2.5, and children with a TNC on the average almost eight times ten to the seventh. The two curves are identical. This slide is two years old. They run now a couple more patients, confirming this difference.

So for adults, the overall survival at that time was 68 percent at a year. And for children, it was 66 percent.

The critical point of this is that all

these patients are fully matched. So a full match will render a very heavy adult to a category of probability of survival that is in the same range as that of children who are in the best possible area of the cell dose.

Now these data are more or less reproducible across the world in different banks and different transplant centers. People are seeing these things increasingly.

But how about the future, and we are plagued with this. I don't know what to do about it. The data in these slides shows that, if we divide our experience in transplants executed at the different times listed there from 1993 to `96, then `97 through `99, then 2000 to 2002, or 2003 to 2005, the first three periods, the data of engraftment is very similar for all those patients, whereas the data for the last period is much better. Engraftment is said to be faster, and is more complete.

The reverse is seen for transplant rates of mortality. The last period is the period in which these complications are less, and the difference is

extremely significant.

So these data, in a way, are consistent with the engraftment data. And now the same is shown by survival. And the most recent period has a survival of the order of 50 percent, up from the previous period in which it was 42 percent.

Now these are evidence that this improvement is not restricted to one group or another. It is present in hematologic malignancies and other conditions. There may be quantitatively different degrees of improvement. We are not sure exactly why. There may be some heterogeneity in the other groups which we will have to analyze deeper. But it is reassuring that it is present across this divide.

And here we have the age effect. On the left are -- I guess I went over the time.

(Laughter.)

DR. RUBINSTEIN: I promise I didn't do anything.

So children and adults both have better prognosis now, as you can see in this slide. The improvement in adults is, in a way, numerically more

remarkable. But percent-wise, it is very similar.

Now approaching the reasons for why this happens, if you look at the lines on the left, those are the geometric means of the cell doses in the four different periods. And the first and second period, the cell doses were relatively the same. But starting in the year 2000, there is a dramatic improvement in the number of cells in each transplant. And there is a further improvement in the last period.

On the right is the levels of HLA matching, with the smallest group being the zero mismatch on the top, and the biggest is the three antigen mismatches at the bottom. The bulk of the differences in the groups with one and two mismatches. And the differences don't seem that dramatic.

But, in fact, it is the combination of these two variables that account for most of the significance of the improvement, but not all. In this slide, there is another aspect for which we have had data now for several years. And that is a comparison of storage in conventional drawers with racks, or in BioArchive freezers where the units can be stored in

a unique position so when you take a unit out, you only take that one unit and you don't disturb anything else.

There is a difference you cannot see. It is almost significant is .0058 or so or 59, but so it is almost significant, but not quite. Yet the data is also hopeful. And I think this ties up with the situation of the transient warming events.

We studied these a few years ago, and we have no doubt as to the deleterious effect of several exposures of short time to the cells in a graft. From a thermodynamic point of view, it is easy to understand that the number of cells can be reduced even if the overall temperature of the graft still is seemingly within the safe range, because units do not warm homogeneously. They warm from the surface in.

Well, we think the data is beginning to recommend that we look at cord blood not purely as a second best when bone marrow or peripheral blood donors are not available. In fact, other than the matched siblings, cord blood is providing results that justify its perfect equality with matched bone marrow,

or even consideration of it as a better source for various clinical reasons that I don't have time to go in. My clinical colleagues are the source of that information, and I'm sure they can do a much better job.

So basically, our message here is that we believe the time is now to begin to look at cord blood perhaps as a first source other than in the matched related sibling donor. And this is another reason to consider that we have reached the end of the beginning of cord blood, and we are entering into the period of maturity for cord blood. The data, I think, at least arguably support that.

We have obtained, if you know, the passage of legislation with the goal of providing at least 80 to 90 percent of all patients with high quality, five out of six or six out of six matches, which provides survivals at least retrospectively in our data equal to or better than the result of bone marrow transplants.

The estimated number of units required, this is somewhat optimistic, but a good case can be

made statistically, 150,000 cord blood units would cover all the major ethnic groups in the United States if the proportions of these groups will become appropriate in the banks.

The way the legislation was drafted and approved, it would lead to self-sufficiently from the recovery of costs to transplant centers. The banks could become sufficient in five years.

This picture was taken when President Bush signed the legislation. And Cladd Stevens, my wife, who is the Medical Director of our program, added the names that President Bush is supposed to be looking at in this picture.

And just to show you some of the living consequences of cord blood transplants, this is Spencer. Spencer had Krabbé -- ALD, I'm sorry, and was transplanted in 2002 at two years. And now has the faintest clinical signs. He is a normal boy. He is going to school. He is doing everything that normal boys do.

And here is Erik who had Krabbé. He was transplanted in 1994 at two years. He is now a

wonderful young man, recovered from a disease that is devastating.

And this is Catalina. She is a Chilean patient shown there in one of the lakes in the south of Chili. She had leukemia at 14. And that was in 2002, also.

And here is Steven. Steven was transplanted at the age of 49. He had accelerating CML that could not be stopped in any way, and was told to go home because there were no donors for him in the registries. And fortunately for him, the people at Hackensack in New Jersey sent us a search request. And we happened to have a perfect match for him. Very unusual.

And he was transplanted, and left the hospital in less than a month, full counts, and manufacturing his own red cells in addition to others. Never had GBH, and is fine today. He had diabetes, and for several years, he did not require insulin. He has Type II diabetes, not the interesting one from the immunologic point of view.

Now so in summary, it has been a wonderful

period in which the prognosis of many patients has changed from very poor to at least hopeful. Any one of us looking at these curves will get the impact of the still very poor overall survivals that we provide for our patients.

Compared to other medical procedures, transplantation of stem cells for these kinds of diseases, we are still climbing. We are in the up of these mountains. But we are now at a point of the mountain that it begins to perhaps appear a little more as a plateau.

And I want to finish by thanking you for listening, but also especially thanking this Agency for having had the foresight to meet with us in 1994, in January, for the first discussions about ways to understand and simulate cord blood transplantation -- banking and transplantation to the mainstream of the regulatory effort in this country.

Thank you.

CHAIR MULÉ: Thank you, Dr. Rubinstein.

(Applause.)

CHAIR MULÉ: Questions for Dr. Rubinstein?

Savio?

MEMBER WOO: Dr. Rubinstein, thank you for this magnificent presentation of all these years and years and years of experience in really pushing the field forward.

My question -- actually I have a couple of questions for you. The first one has to do with the slide that you showed on the donor selection preferences that you are recommending for a change. One, two, three, four -- kind of changing the orders around.

I totally agree with you that the first preference should be the matched adult related, but I don't quite understand, why are you recommending that the matched adult unrelated, number two, should be downgraded to number four.

I have no issue of say using the matched cord blood unrelated. That should be preferential to the adult, because cord blood is better than adult, but I don't quite understand why the one or two unmatched cord blood, unrelated, would be more preferable to matched adult unrelated.

DR. RUBINSTEIN: Thank you very much for this question. It is interesting. The data show that, with all probability of survival, et cetera, is very similar. There is no statistical difference. And there being no statistically significant differences, the preference for cord blood, in my opinion, should follow from the logistic improvement that is obtained when you don't have to search for the living donor. You don't have to accommodate to his health and so forth.

MEMBER WOO: Okay. Can I follow up for a moment? Another question I have for you is that you show your results for the cord blood transplant for genetic diseases, there were 400-and some cases. And then you just lumped them together in one outcome.

I was wondering, you know, because you are dealing with different genetic diseases and many, many different kinds, do you see differences in terms of outcome? Or the numbers are too small for you to break them down?

DR. RUBINSTEIN: Well, the genetic diseases are the ones that I listed. They are not --

it is not every possible genetic disease that ever was treated. And, in fact, we know that it doesn't work so well in some diseases.

MEMBER WOO: Yes. What are the ones that work better than, and what are the ones that don't work so well?

DR. RUBINSTEIN: Right. That is an issue. And we have good data for the diseases that I listed. And for those we've failed to detect heterogeneity, but there are others that have been tried, and which attempts at transplantation doesn't work, or doesn't appear to work. At least we haven't learned how to do it. One of them is Lesch-Nyhan. It's not working so well. And Tay-Sachs is somewhat --

MEMBER WOO: Okay. So some of them with neurological --

DR. RUBINSTEIN: -- disappointing.

MEMBER WOO: -- work. So thank you very much.

And my final question to you would be, in all of these years of experience of over 2,000 transplants, could you comment on the incidents of

GVHD and the potential toxicities?

DR. RUBINSTEIN: To summarize on GVHD, that was one of the original reasons why we wanted to try cord blood, because it was felt from the data in sibling transplantation that occurred in the period between 1989 and 1992, we felt that there was enough evidence there that even mismatches resulted in lower graft-versus-host disease.

And that has been confirmed in large measure. It is not that there is no graft-versus-host disease. There is sometimes very severe graft-versus-host disease. But statistically, and in general, the severity of the graft-versus-host disease, and particularly in the chronic phase, is lower.

MEMBER WOO: Thank you.

CHAIR MULÉ: Dr. Kurtzberg?

MEMBER KURTZBERG: I have a few comments, and then a question.

First of all, Pablo, I want to thank you in particular for mentioning the non-malignant diagnoses, and the indications for a cord blood transplantation in that disease category, because

these are under-served patients, generally young children, with orphan diagnoses that really should not be ignored. Cord blood has an incredibly unique niche for helping these kids, both because it may correct certain genetic diseases better than adult cells, and also because it is readily available, and frequently timing is very important in proceeding to therapy.

In answer to the previous question, in the leukodystrophies, cord blood has a remarkably beneficial effect if transplantation is performed in children before the onset of significant symptoms. So in Krabbé, ALD, MLD, Kroller, Hunter, and even Tay-Sachs, if transplantation is done early in the course of the disease, and that is going to vary based on infantile and juvenile forms, the results are dramatic.

On the other hand, if transplantation is performed when the child already has symptoms, the results are not as good. Life is prolonged, but the quality of life is not improved.

But I think that, as a Committee, we really have to consider the indication question,

because this would be a great oversight if it isn't part of the initial licensure.

Secondly, I wanted to ask a question about whether you think HLA mismatching has an impact on relapse, particularly in ALL or some of the other acute leukemias. Because even though you listed the algorithm of, you know, matched-related donor first, and then cord blood and then unrelated donor, I think cord blood could potentially offer an advantage in protection against relapse. And I wonder if you could talk about that.

DR. RUBINSTEIN: The data is not definitive on this. We will need a lot more data to be certain of that. But there is some experimental work going on that shows that if you take into account the natural killer cell concentration and effect in cord blood, the main consequence of this is the rapid improvement and the -- I hate to say definitive, because the time is not very long -- the improvement of the probability of remission in patients with refractory leukemia and repeated inductions, and so on. There is a tremendous amount of hope in this

particular approach, because the function of natural killer cells can be thought of almost tailored to execute the function that Joanne just indicated.

So the fact that we have, in cord blood, the potential to manufacture many more natural killer cells than are detectable with the conventional tests, and presumably this happens in vivo after engraftment, this could be thought of, not just as a replacement and manner of reconstituting the patient, but also of providing something special additional different from what we can get from adults, although we do get, now, evidence that there is an effect in adults, as well, particularly in acute myelogenous leukemia.

CHAIR MULÉ: Dr. Horowitz?

MEMBER HOROWITZ: Thank you very much. Wonderful presentation, and it didn't matter that there weren't lines. Really you could see everything pretty much.

I think that we need to distinguish between what diseases hematopoietic stem cell transplantation in general is good for, versus differential activity of cord blood versus adult donor

transplants, because the statement you made that transplant doesn't work so well in Lesch-Nyhan, well, that doesn't matter whether it is a cord or whether it is a bone marrow. And I don't think that there is any instance in which we see a differential outcome between cord blood and bone marrow.

I mean the things that bone marrow works well for, cord blood works well for. The things that bone marrow doesn't work well for, cord blood doesn't work well for. So I think we have to keep that perspective.

And I think -- I agree with Joanne that this whole issue of having the indication include nonmalignant diseases is very important, because actually a higher proportion of cord blood transplants are being done for nonmalignant diseases than adult donor transplants.

Overall, about 30 percent of unrelated donor transplants are for nonmalignant diseases, and if you look at cord blood transplants in children, 40 percent of them are for nonmalignant diseases according to data that is registered with the CIBMTR.

So I think that it very much parallels the efficacy of adult donor transplants.

My question to you, Professor Rubinstein, has to do with the improved outcomes. And we all know that -- we like to think that the things that we do make a huge difference for our patients. But, in fact, much of the prognosis of patients is due to things that we, unfortunately, can't do anything about.

And having looked at the change in disease status over time, one of the big changes over the past five or six years is that people are starting to use cord blood -- think of cord blood as a graft source earlier in the course of disease.

DR. RUBINSTEIN: That is very true. We cannot see a major difference in terms of the classical classification, so to speak, of the degree of advance. But indeed, there may be smaller gradations that are critical, and that we are not measuring. Perhaps there may be better ways of ascertaining the data that will allow us to discriminate better, or to do better analysis.

Anyway, I would very much like to collaborate with your group again in trying to tease that apart. But I think that just the availability of faster transplant, once the decision is made, is itself a very good reason why there should be an improvement.

And the interesting thing is that these cord blood cells were available just as easily before 2003, I guess. And yet we see the effect. And it is a very easily measurable one.

So the only thing I can do is hope that it keeps getting better, even if I don't know exactly the reason.

But thank you very much for your offer to help us to tease this out.

CHAIR MULÉ: Dr. McCullough?

MEMBER McCULLOUGH: Pablo, first of all congratulations on your role in getting us to where we can have this discussion today.

My question is, the slide that you showed showing the differences in zero, one, two, and three mismatches, some of your comments implied that you can

tell the difference between whether that is an AB mismatch or a DR mismatch. Do you want to make any comments about that?

DR. RUBINSTEIN: Yes, we have done it in all those different ways. And the results are the same. Numerically, however, and this is very interesting, numerically, we don't see a significant difference between an A or B mismatch and a DR mismatch. It was a little surprising to us.

The one thing that is persistently there is that two DR mismatches seem to be matched worse than two B mismatches or two A mismatches. Or worse than an A and a B mismatch combined. So there is something different about DR that way.

But everybody sort of intuitively runs away from two DR mismatches. So I believe we have very few of these cases.

CHAIR MULÉ: Dr. Laughlin?

MEMBER LAUGHLIN: I would also echo appreciation of an excellent, thoughtful review of the data.

My question is focused on your explanation

as to the increase in geometric mean of total nucleated cells contained in units during the time period 1993 to 2005. In other words, is it related to collection, processing, unit selection, all the above?

DR. RUBINSTEIN: It is the criteria for inclusion in the inventory, in the search inventory. Starting around 2000 or so, we started to look for ways of ensuring a consistently higher minimum cell dose available, and have progressively increased that minimum cell dose.

The combination, first of cell dose and HLA, seemed very clear because, if you look at the cell dose in the period of 2000 to 2002, it was dramatic. We went almost double in many cases. And yet the clinical results in that period were not all that better. There was no significant difference.

But at the same time that the cell dose became better, the HLA matching became worse during that period. And so what we gained on one side, we sort of let loose on the other. And right now we are coming back to gathering the two things, and now things are working better.

But it is not enough. As you saw, this freedom from the thermodynamic effect of exposure to heat has helped somewhat. We are not statistically definitively safe in that conclusion, but we are very close to it.

And it is a logical conclusion to take a unit from minus 196 and put it at room temperature, 20 degrees centigrade, is like putting your hand into boiling oil. Of course, if you withdraw it quickly, nothing major will happen. But if you leave it there for more than a few seconds, you will feel the difference. And the same happens here.

The cells that are in the periphery of your bags will suffer the most. And with time, if you repeat this exposure several times, you will get those cells killed or ineffectual. So I think we are on the way to understanding one other aspect of this situation.

But there maybe still further ones. And the effect of an overall improvement in the clinical treatment of these patients may also be a part of this.

By the way, the data does not show that non-myeloablative regimens are the cause of this retrospective improvement -- the retrospectively ascertained improvement. We have a substantial increase in the number of patients that are treated that way with non-ablative treatments, but they don't seem to be the cause of this phenomenon.

MEMBER LAUGHLIN: My second question is focused on single versus double units in adult patients. You had not included that analysis in your presentation. And fully recognizing the CIBMTR prospective studies to ask the question of one versus two units in adult ablated patients, I'm interested in your comments as to analysis by retrospective study of comparisons in ablated patients of use of single unit versus double unit.

Recognizing that analysis done at a single institution, is there any data in the multi-institution datasets, either in the United States or Europe, to look at this question?

DR. RUBINSTEIN: I am not aware of another one. Unfortunately, there have been a number of such

transplants in many places, but each one of them has few of them. The second institution to do a large number is Memorial Hospital in New York. They have done now over 20 such transplants. They seem to be extremely happy, but that is just 20.

We don't have the data for all of them, because some of the data come from transplants done with units of other banks. One of the great aspects of the maturation of cord blood is, of course, the availability of units across the world from many banks, improving the chances for patients to get a better match.

Now, I have a thought about using two units. It may be not a very nice one, but I believe two units are better than one because there is a fraction of units that will not engraft. We don't know the reason, really, but there is a certain number of units that are associated with lack of engraftment.

And without prejudging why that happens, if you use two units, the probability that both will fail to engraft becomes smaller. And so you should expect an improvement just on that basis.

And beyond these obvious, or at least it seems to me an obvious explanation, beyond that we will need a lot of data to see further rationale for this.

MEMBER GERSON: Pablo, I want to compliment you as well on what will become, for us, an incredibly important database, both historically and to compare going forward.

If I could just make a comment, what most impresses me is the lack, in the database, of any way to validate based on randomization of the relatively qualitative case series data. And at some point, we're going to need to deal with the issue of how do we compare Group A to Group B other than by historical case series.

I was going to ask you about the ablation data, which you qualitatively gave us an impact on, but again, it would be very nice to know just how much the change in preparation of the patient population that undergo transplant is impacting on the improvement in survival.

I'm very concerned, because our task here

is to look at the specifications of the product, that we be as firm as we can with improving the quality of the product, potency, et cetera. You've advised us on the two different major freezing modalities that are now most commonplace. And a p-value of .058 is pretty close, as you said, to statistical significance.

What do we do with the existing bank that is in vats of variable ages? Do you have a suggestion for the Committee on these banked samples?

DR. RUBINSTEIN: It's difficult to make a recommendation which requires judgments of many different kinds, not just the probability of damaging cells. But I guess at some point, we will have to obtain a direct measurement of the proportion of cells that are not going to work when transplanted.

And there are some hopeful signs that we may define such methods. Most of the evidence comes from data on apoptosis. But it is still early for me to go into much detail, just to say that there are quick ways to define apoptosis in earlier moments.

The trouble will be in the clinical justification of any such measurement, because

obviously you would have to undertake a very large study across many different banks and transplant centers, in which these measurements can be done in a standardized way before freezing and after thawing.

And at least after thawing, we might approach some way of answering these questions. We are doing this work because we are concerned. We also have some units, particularly older units, in which there is no freedom from these transient warming events.

Before the BioArchive, we had to use the same as everybody else, racks with things. And with racks, every time you bring it out to put one in or to take one out, the others suffer just as well. So even if you are very careful, even if you keep everything in the gas phase, you still incur these problems.

MEMBER GERSON: Could I just further ask, is there any -- are there data to suggest that age of unit impacts on outcome?

DR. RUBINSTEIN: We don't think so. In our data, the units from very early are just as good as new. We have done transplants this year of units

collected in 1993. There have been three such transplants this year, more than last year at this time of the year. But of the three, one is very recent. The other two engrafted quickly.

CHAIR MULÉ: Doris, did you have a question?

MEMBER TAYLOR: I wanted to follow up on the two unit question that Dr. Laughlin asked. You said that you think that maybe there is less likelihood of failure if you transplant two units.

Although that could potentially explain why one unit is perceived to outgrow the other, I'm concerned. Does that imply, in some way, that actually transplanting two is bad for -- I guess my question is, is there an interaction there we don't understand that could actually be deleterious?

DR. RUBINSTEIN: That, I think, is a very perceptive question. Overall, I believe the fact that you have two chances improves the situation. But it is possible, when you transplant two units, one of which, let's say, is a good match with a low cell dose. The other a poor match with a high cell dose.

And let's say you get engraftment of the poorer match, you may be decreasing the overall chances of that patient that would have been better had the better-matched unit stayed on. So that is a potential possibility.

The other is that the mechanisms of winning and losing this battle between the two units are unclear. They still -- we still don't know why that happens, although there are hopeful signs that we will understand this in the near future. But we really don't know yet.

And so there is hidden there a potential for an interaction which may be damaging. We may be wiping out, for example, the natural killer cells of one with the other.

CHAIR MULÉ: Mary?

MEMBER HOROWITZ: I think in terms of the single versus double cord question, we have to remember that most of the double cord blood transplants have been done in patients for whom a single cord blood transplant was not possible, usually because it is a large patient who needs it.

And so comparing the results in that population with single cord blood transplants, you have two really different populations. And I think Professor Rubinstein has also already pointed out that the numbers are really small.

So, you know, in that it allows patients who couldn't otherwise have a cord blood transplant to have one, that's fine. But to say anything relative to the other -- this is, by the way, one area where there is a randomized trial going on of single versus double in children who could possibly get either one.

CHAIR MULÉ: Bill?

MEMBER TOMFORD: Thank you. That was an excellent presentation.

What is the age of your inventory? In other words, do you have a lot of units that are very old? And do you go through and cull these units occasionally? Or how do you keep your inventory?

DR. RUBINSTEIN: Yes. Our inventory started in 1993. The first unit was collected the second of February that year. We have still approximately 2,000 units from the period 2003 to

2005.

In 2005, we began the replacement of the old method, which consisted simply of cryoprotecting whole cord blood, and just freezing it. We changed that procedure for one in which we reduce the number of red cells. We eliminated about 90 to 95 percent of all red cells, and were able to freeze smaller volumes, exactly 25 milliliters with cryoprotectant, which allowed us to compute very accurately optimal curves of freezing, and remove the freezing procedure as a variable in the quality of these units.

We have also about 5,000 such units from the second period. The third period is the arrival of the BioArchive. And in that period, we have stored approximately 28,000 units. So we do have a sizable number of older units. But since 1999, we have assembled the vast majority of our inventory.

We do conduct every year a review of the old units, and we test colony forming and CD34 viability for units that were collected in 1993. And so far, we have not detected any difference from what we observe now on fresh units that are frozen and

thawed. The numbers are almost identical.

So I don't think that the storage, if it is done correctly, will have a major influence. You can store for many years.

One of the interesting aspects of the FDA position with regard to stored cord blood is that we will be able to show them our data for the different periods, and then the recommended maximum storage period can be amended.

There is a wonderful spirit to understand and take into account the evidence in making these decisions so that they don't become inhibitory of the progress in the field.

CHAIR MULÉ: Stan?

MEMBER GERSON: I have just one quick question to follow up. Is there a reason, in your mind, to take an entire unit and assay it for quality assurance? Is that a guideline of interest to the question of the guidelines?

DR. RUBINSTEIN: I'm not sure. You mean to take a unit, thaw it, and then do all of the measurements on that thawed unit? Well, I think it is

a kind of necessary thing to do if you want to know that your estimates of what is there, in fact, are there, because we, as well as all people that work in cord blood banking, have found reports from the transplant center that say that our unit had fewer cells.

We also have received reports that they have more cells. When we do the thawing in our bank, we don't find these major differences. So it is clear to us -- to me, anyway, that the technical aspects are very important, and they should not be minimized.

The technical requirements at the level of the transplant centers' stem cell laboratories are very strong. I have seen, in one case where I went to help do the first transplant, I have seen people just leave the unit on top of a desk while they entered the data, and did all of the other necessary paperwork for several minutes despite my protestations that that is not something to be done.

So these are things that happen. It is less important with large volumes. If you feel the half a liter of peripheral blood stem cell suspension,

well, the losses will be, percent-wise, much less noticeable. But with smaller transplants, the precautions should be maximized.

And here I believe the accreditation procedures should be strengthened, and made much more rigorous.

CHAIR MULÉ: One final question. Dr. McCullough?

MEMBER McCULLOUGH: Actually, it has to do with the same point. I'd just ask if, Pablo, if you agree that sacrificing an entire unit is not as big a deal as it would seem, because a large number of the units that are collected end up not being suitable for clinical use. So you have an ample supply of full units to do testing on if that is appropriate. Do you agree, Pablo? It's not as big a deal as it might seem.

DR. RUBINSTEIN: Yes, I agree with that conclusion. We don't have that many frozen that are not going to be used, for two reasons: we weed out as many as possible before we freeze; it is quite expensive to freeze and do all the testing and so on.

But in addition, we don't like to have in the freezer what some people consider duds. It is not a good idea.

So we do have some units that are perfectly good, and they are kept. And these are units where the mother originally granted informed consent, and then later on, at some point, for some reason, no questions asked, the mother decides that she doesn't want to be in the program, and that she prefers that the unit be used for research or quality assurance or other things.

But I am fully in agreement with your statement. It is not difficult for a cord blood bank to have units fresh and frozen to answer your question. We can do that very well.

CHAIR MULÉ: Great. Thank you so much, Dr. Rubinstein.

What I'd like to do is take a 15-minute break and have everyone back here at 10:45. And we'll begin with the open public hearing.

On behalf of the Committee, I'd like to thank Dr. Lazarus and Dr. Rubinstein for their very

nice and thoughtful presentations.

(Whereupon, the foregoing matter went off the record at 10:33 a.m. and went back on the record at 10:49 a.m.)

CHAIR MULÉ: Okay. I'll start by reading the FDA statement and that is open public hearing announcement for general matters meetings.

Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee Meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting. For example, the financial information may include the company's or a group's

payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

So with that, we'll go ahead and the first speaker for the open public hearing is Joseph Giglio.

MR. GIGLIO: Good morning. I have no financial things to claim. I'm a paid employee for AABB.

AABB thanks the FDA for this opportunity to provide a statement on the draft guidance for cord blood licensure. We would like to commend the FDA on the time and effort that they expended in drafting this draft guidance.

During the review of the draft guidance, we noticed a few areas that we believe should be revisited to provide clarity for the personnel that will be ultimately responsible for implementing the

guidance. The guidance document does an excellent job of outlining what required and recommended tests should be performed for the licensed products but not for the products previously manufactured.

We are pleased the Committee has been asked to discuss the types of data that could be submitted to demonstrate comparability between the previously manufactured HPC-Cs and the HPC-Cs manufactured currently. There are thousands of products in inventory which are acceptable but may not have had the recommended tests performed.

We would also ask the FDA to consider what mechanisms might be available to release these products for transplant in the event that they cannot be demonstrated to be comparable for purposes of licensure.

Another issue that has not been addressed is products from Europe. Approximately 20 percent of the cord blood products that are transplanted in the United States originate from Europe. Products that are collected in Europe may not have had the required and recommended tests performed. And the products may

not be licensed by the FDA.

It is of great concern that the European facilities may not want to pursue FDA licensure for their products. If this becomes a situation, how does FDA envision the continued use of imported products?

We applaud the FDA for the flexibility that they have allowed in the draft guidance in areas that permit the flexibility. However, we did find two areas where flexibility should be incorporated.

The results of hemoglobinopathy testing is not dependent on when the cord blood sample is collected, i.e., pre- or post-volume reduction. But according to the draft guidance, only the pre-volume reduction sample is acceptable. Therefore, we recommend that the appropriate sample type be modified to include the use of a post-volume reduction sample.

Also in the draft document it is recommended that the validation summary include data from the manufacturer as well as the thawing and cryoprotectant removal. While we agree that the processes to be performed must be validated, not all facilities will perform the process of cryoprotectant

removal.

Different protocols, procedures for administration of HPC-Cs may or may not require the removal of cryoprotectant prior to administration. There is usually very little DMSO in an umbilical cord blood unit. And only patients under approximately 15 kilograms would potentially need to have the product washed. Therefore, the requirement to validate the process to remove cryoprotectant should be clarified so that the process is validated only if the procedure is performed.

The draft guidance document states that sterility of these products must be performed using the testing methodology defined in 21 CFR 610.12. As the Committee is aware, many of the cord blood banks are using one of the automated methods for sterility testing.

Please comment on the necessity for validating the automated method versus the CFR method. If required, please comment on the validity of submitting a collaborative validation study from multiple banks which could then be used by all banks

for justification for not doing the CFR method.

The proposed requirement for the labeling of products with an NDC number raises series risk-benefit concerns. This has been previously addressed with comments to the docket in response to the August 29th draft guidance requirements for foreign and domestic establishment registration.

It is our position the NDC system is not a good fit for cord blood products or other therapeutic cells and that manufacturers and consignees worldwide receiving them for patient infusion and/or transplantation are already implementing a system that was developed specific for them.

The system that has been voluntarily accepted by the international cellular therapy community is ISBT 128 Standard. The community has invested much time and money in developing this system as well as implementing plans.

A careful review of the facts indicate that the use of the NDC numbering system in addition to the already existing ISBT 128 system does not offer

any increase in patient safety. In fact, we argue that implementing the NDC codes for cord blood products and other therapeutic cells would hinder the progress of implementing the superior 128 information standard for these products.

We request that FDA carefully consider patient safety issues when evaluating the requirements for NDC codes on these products for ultimately having to utilize two different labeling systems will negatively impact patient safety and provide opportunity for increased errors during the manufacturing process.

If the primary purpose for the use of NDCs in cord blood products is to maintain a list of manufacturers and their products, we propose that the information could be captured more efficiently and economically via a modified facility registration form.

We believe the NDC system is not a reasonable option for improving the safety of cord blood products and that these products should be exempt from the requirement.

Regarding the final question to the Committee today, we believe that a set of recommendations for HPC-A, similar to what has been proposed for HPC-C is appropriate to demonstrate safety and efficiency of these products.

The majority of these comments presented today are the result of an inter-organizational work group consisting of AABB, International Society for Cellular Therapies, and the National Marrow Donor Program. Overall, the work group believes that this is a comprehensive and well-prepared guidance document.

The work group's comments on the draft guidance document will be submitted to the docket by the close out date.

And again we want to thank the Committee for the opportunity to make this presentation today.

And to the Executive Secretary, we commend the FDA for drafting guidance for the preparation and public availability of information given to the Advisory Committee members. We believe it is important for the information to be publicly released

as early as possible.

The ability to prepare a focused presentation for today's open public hearing was dependent on knowing what the Committee is being asked to consider. In cases such as today where the information would be considered to be exempt from disclosure under FOIA is to be discussed, release of the briefing information and questions to the Committee prior to 48 hours would have been beneficial to the Committee's consideration of all applicable information.

CHAIR MULÉ: Thank you.

Next up is Dr. Butterworth.

DR. BUTTERWORTH: Good morning. I appreciate the opportunity to be here and speak about the cancer risk associated with ethylene oxide in the processing of cord blood. And if you will excuse me. I have a cold that went straight to my voice today.

I am a paid consultant for ThermoGenesis Corporation. But the opinions I'm presenting are mine alone and were not influenced by ThermoGenesis.

Stem cells and cord blood are used to

repopulate the bone marrow in chemotherapy patients. This is a process importantly involving extensive cell division. First of all, these cells have to find their way to the bone marrow and then divide extensively to repopulate the bone marrow.

Then these are going to be long-lived, continuously dividing cells that create all the hematopoietic progenitor cells for the lifetime of the patient. These are critical cells, very important. Absolutely no mutagenic changes are acceptable that could yield precancerous or cancerous cells.

Ethylene oxide is a proposed sterilant for cord blood processing disposables. The FDA in their guidance is proposing a residual value of five milligrams per disposable of ethylene oxide. Ethylene oxide is a potent, direct acting, DNA-reactive mutagen and clastogen, that is it breaks chromosomes.

In studies it has been shown to produce lymphoma and/or leukemia in mice and rats. And in epidemiology studies, the same endpoints in human beings. Thus, these hematopoietic DNA cancer target sites are, by definition, subject to mutagenic attack

by ethylene oxide.

There are serious susceptibility concerns. The stem cells would be directly exposed to the DNA-reactive mutagen ethylene oxide during processing without any anatomic barriers or detoxification mechanisms. So when you think of cancer studies and risk assessments for ethylene oxide with animals or human beings, you have to realize that there is a lot of protection. The chemical has to get taken up by the body. There are a lot of barriers before it can get to the bone marrow. There is a detoxification mechanism in metabolism, detoxification excretion, few of which are present in the current situation that we're talking about.

In addition, the proliferating cells are highly susceptible to mutation induction by DNA-reactive agents. There is no worse combination for inducing mutations and cancer than a rapidly proliferating cell population in the presence of a DNA-reactive carcinogen.

To show you how serious this is, mouse lymphoma cells grown on plastic culture flasks

sterilized with ethylene oxide resulted in mutation frequency increases of six- to 14-fold compared to the same flasks that are simply autoclaved for sterilization.

So what has happened is the ethylene oxide absorbs into the plastic. And then the cells are in direct contact with the compound and there is the increase in mutation frequency.

There is no safe dose of ethylene oxide. Current FDA guidance would allow concentrations in the range of 30 to 100 micrograms per mil. of ethylene oxide in cord blood preparations. And these values are easily in the measurable range of mutagenicity in DNA-damaging assays. You can measure DNA damage at values of less than one microgram per mil.

There are no data available that demonstrate the safety of these concentrations or any concentration of ethylene oxide for stem cell exposure. FDA and EPA cancer risk models recognize no safe or threshold dose for direct-acting mutagens.

Fortunately, there is a straightforward alternative. The cancer risk of ethylene oxide can be

eliminated simply by the use of gamma irradiation or steam for sterilization of all products for cord blood processing and storage. Units of stored cord blood exposed to ethylene oxide should not be used without the transplant physician being made aware of the exposure and of the potential consequences of that. And possibly new labeling for ethylene oxide exposed cord blood units should be considered.

I have been doing genetic toxicology and chemical carcinogenesis research for 30 years and I must say this is not a good idea to have ethylene oxide present. Given the choice, I certainly would not want my child given stem cells that have been exposed to ethylene oxide.

But fortunately there is a straightforward solution. And I think that is the way that things should go. And I would urge the FDA to change their guidance to go with this more safe sterilization methods.

Thank you.

CHAIR MULÉ: Great. Thank you.

Next up is Dennis Confer.

DR. MILLER: I think the first thing you will notice for some of you is I'm not Dennis Confer. He apologizes. He was not able to be here today. And I have no disclosures other than the fact that I am an employee of NMDP. And likewise would like to thank the Committee for the opportunity to make some comments.

I have three issues we'd like to talk about in my few minutes is that in the regulation of PBSCs or HPC-A, the safety and efficacy of unrelated donor PBSC and related donor PBSC as well as bone marrow are very similar yet they are regulated differently under either 351, 361, or in the case of bone marrow, under HRSA.

And if we're going to look at licensure of PBSC, the requirements should reflect that we've seen with the current data and safety so that it is feasible to implement in the different types of centers that exist. Unlike blood centers that may collect tens of thousands to hundreds of thousands of blood products, many apheresis centers that collect PBSCs may collect less than ten per year.

And then the third point is that importation of PBSCs is essential to meet the needs of the patients who need transplants in the U.S. and that the regulatory framework needs to allow continued importation of these products without becoming burdensome for the same reasons as in bullet two.

So one way that we propose this could be handled would be that the related and unrelated PBSCs could be treated alike. Those that are minimally manipulated for homologous use, HLA matched, and used for hematopoietic reconstitution could be handled in the same manner and related donor PBSC. And that would also include DLI or therapeutic T cells.

And the reason that we think that would be a possible approach is in looking at PBSCs, really the relevant issue is control of communicable disease. These products are very different than traditional biologic drugs. They are patient specific. They have a very high degree of HLA matching. And so there may be one or at best a few donors who match a particular patient.

They are minimally manipulated after the

apheresis collection and infused ASAP without cryopreservation, minimal processing, there's minimal manufacturing. The quality of these products is uniformly high. So when we look at manufacturing, there are not a lot of variables that impact the quality of the product. And really in the situation where we have the patient who has been either myeloablated or received reduced intensity condition, the product really needs to be infused or the patient is likely to die.

So we think that one possible approach is to regulate these products under 361 and the GTPs would adequately control the risk of communicable disease.

Moving on to kind of the second point is looking at our apheresis centers that collect these products. We have 88 registered within the U.S. who collect PBSC and DLI. Seventy-two percent of these are hospital based. They're not in a blood center. And three of 63 are licensed biologic establishments. And that these establishments collect more than three-quarters of the products that are used for patients in

the unrelated transplant setting in 2005.

And so the concern we really have is the last bullet. If they don't collect very many products per year, as I said maybe less than ten in some cases, will they continue to do collections for unrelated products and not go for licensure. And, you know, the question being well maybe the donors would be willing to travel. But, in fact, we have experience with, in fact, not all donors are willing to travel.

So the concerns are that fewer sites will collect these products both domestically and internationally. Donors might need to travel to distant collection sites and their participation might decline. The cost for collection will go up. Importation of these products might go down. And really the bottom line and the most important thing is patients may not get the best HLA-matched product for their transplant.

And then the third point I'd like to address is why importation of PBSCs is so prevalent but also so essential. And it really comes down to the simple fact that the need for HLA matching drives

the international exchange of these products.

And here is some data from WMDA for 2005. And it looks around the world and you can see it really is a global issue of products that are collected in one country and where the patient is who receives those stem cells.

And you can see that 39 percent of products have the donor and the recipient in a different country. So this really is a global need in the transplantation community to have products that can cross international borders.

So in conclusion, we suggest that unrelated PBSCs could be regulated under 361 based on their safety and efficacy data and that the primary risk is the risk of communicable disease. Alternatively, if licensing requirements should reflect the current understanding of PBSC safety and efficacy and not be so burdensome as to risk the loss of PBSC collections by some domestic and international apheresis centers.

And that any proposed regulatory framework needs to accommodate importation of products essential

to meeting the needs of patients for HLA-matched stem cell products for transplantation.

And with that, again, I'll thank the Committee for your attention and the opportunity to address you today.

CHAIR MULÉ: Thank you, Dr. Miller.

Doris, you had a question?

MEMBER TAYLOR: Of the global donors, what percentage are produced in the U.S. for export versus the converse?

DR. MILLER: Actually that is a great question. If you look at the United States, kind of the units that go for export versus import, the numbers are almost identical. And, in fact, I think in 2005 they were numerically equivalent -- exactly equivalent. So it is a fairly equal exchange.

CHAIR MULÉ: Did you have another slide set?

DR. MILLER: Yes, I do because I'm going to do the one I was supposed to do. But I don't think -- am I next in order?

CHAIR MULÉ: You're next in order, yes.

MEMBER LAUGHLIN: Dr. Miller, second question.

DR. MILLER: Yes?

MEMBER LAUGHLIN: Does NMDP have analysis of quality of products at those apheresis centers that do less than ten collections per year versus centers that would meet licensure requirements?

DR. MILLER: That's a great question. And we do have some data, for example, on efficiency of the apheresis collection. And it does vary between center. But when you look at do you actually collect enough cells for transplant, we really do.

So there's kind of two answers to your question. Yes, we do have that kind of data. But it looks like in the smaller centers, we do have adequate collections.

MEMBER LAUGHLIN: And no differences in sterility or other aspects of product quality?

DR. MILLER: Not that we've seen, Mary.

Okay, no financial disclosures again other than working for NMDP. And now I would like to talk back to the topic of cord blood banking. And, again,

have three issues I'd like to present to this Committee.

And one concerns what I'll call the retro units or those prior to licensure and how we are going to continue to make those products available for transplantation. They're a large percentage of the inventory and we need to be able to address that issue.

The other issue that has been brought up in Pablo's presentation and questions afterwards is the indications for cord blood transplantation need to be broadened to include nonmalignant conditions.

And importation of cord blood units is essential to meet the needs of U.S. transplant patients. And we need to continue to allow those products. And I'll show you a little bit of data on that as well.

When we talk about the current or older inventory, it is a large fraction of the inventory today. And even as we look at continuing to increase the inventory with the new federal support, we still have an inventory that while it is large, it doesn't

have enough to get a five of six, six of six, what we think are better HLA matches for all patients.

One of the key issues is documentation of retrospective equivalent GNP might be difficult or not possible for some cord blood banks. And then how would we distribute these units if they are available. Would they be distributable under a perpetual IND or some other mechanism? I think it would be fairly easy to document comparability on the biochemical parameters. But the GNP may be more difficult.

And that our data indicates that older units actually have similar clinical outcomes to units collected more recently. And here is some data on that. If you look at our inventory, 80 percent of the inventory in the NMDP cord blood network was collected before 5/25/05.

So that's an arbitrary date but it gives you an idea that a lot of the inventory are older units. And over 90 percent of the units that have been used for transplant were collected in that period of time. So I think we need to have these units available.

And there are actually two curves here that look, again, with the date of 5/25, before and after that date, the survival from the cord blood transplants facilitated through NMDP, the numbers after 5/25 are a little bit smaller. But as you can see, it looks like the survival is very, very similar. And engraftment has a similar shaped set of curves.

The next point I'd like to address is transplant for nonmalignant disorders. And our numbers are similar to those that Pablo shared with us from New York is a little over a quarter of the total transplants actually facilitated through NMDP are for nonmalignant disorders.

And if we're going to have these units available for off label use by the transplant centers, if we do that, are the cord blood banks responsible for how the transplant center physician uses the product after it is shipped? This question was also addressed earlier. The indications for specific nonmalignant disorders are rare. How can we move from an IND setting to licensure?

And our data suggests that there are

similar outcomes for transplants for both malignant and nonmalignant hematologic disorders, again in that broad separation of the two categories.

And this looks at the survival when we look at the data between nonmalignant disease indications and hematologic malignancy indications. And you can see that they are statistically the same.

The third and last point is the importation of cord blood units and, again, we need to have these units available to meet the needs of the U.S. population for the best HLA match. It is a large proportion of the units used for transplantation in the United States.

And the concern here is many of the international banks only ship a few units and may not apply for licensure. And I think Pablo showed a nice graphic of the world for his bank of where the units come from. And, again, many countries only hade a few that were imported into the U.S.

And a similar issue for PBSCs. If we're going to import these, how do we do that? Is this a perpetual IND for cord blood units that are not

licensed?

Just to give you an idea of the amount of units that are imported, this is for calendar year 2006, 19 percent of the units imported into the U.S. were imported into the U.S. and within the NMDP network, a similar percentage, 14 percent.

And then in summary, existing cord blood units, those that will be prior to the licensure date and are not able to meet the licensure requirements need to be available for transplantation. And here I think the key issue is the retrospective documentation of GNP for licensure may be unlikely for some of the banks.

Indications for cord blood transplantation need to be broadened to include nonmalignant disorders. And finally importation of cord blood units really is essential for U.S. transplantation patients for hematologic transplantation.

And with that, again, I thank the Committee for the opportunity to share some thoughts. And will take questions if that's what we --

CHAIR MULÉ: Thank you. One or two quick

questions?

DR. MILLER: Yes, Mary?

DR. LAUGHLIN: With respect to importation of cord blood units and the reasonable requirements of CLIA accreditation, what is NMDP's experience in a working model in conventional allogeneic grafts that might be applicable to cord blood with respect to CLIA requirements?

DR. MILLER: Good question. For CLIA, I'll kind of break it into two types of international centers. Those that are in Europe may have a CLIA-approved facility that they have access to. When you get outside of Europe, that gets much, much more difficult.

And so now you are getting into the eligibility/ineligibility requirements. And so in the adult setting, we still have products coming in that would be labeled ineligible because testing wasn't performed in a CLIA-approved lab.

MEMBER TAYLOR: Likewise, is there -- with regard to importation of units, is there any evidence of increased adverse events with importation? Or

failure to meet requirements -- sterility requirements?

DR. MILLER: We haven't seen that. Have you, Pablo? Any quality control issues with units coming from other countries?

DR. RUBINSTEIN: We don't see those units.

MS. DAPOLITO: Dr. Rubinstein, could you use the microphone, please?

DR. MILLER: He's saying he doesn't see those units.

CHAIR MULÉ: Dr. McCullough?

MEMBER McCULLOUGH: It's a continued version of the same issue, John. Does NMDP have some criteria or a way that an international center applies and is somehow certified by NMDP to meet some basic quality standards of some sort? Apart from CLIA testing, there must be some way you decide whether you are going to be willing to import a unit from another donor site.

DR. MILLER: That's a great question, Jeff. Thanks.

We actually have two basic ways that we

qualify -- whether it is adult or cord blood banks, one is being actually a center for us and the other is the cooperative registry model. But both require an application process, review of quality requirements, a site visit by us. So, yes.

MEMBER McCULLOUGH: So those quality requirements could be shared with the FDA, I assume, if they don't already have them?

DR. MILLER: Yes.

CHAIR MULÉ: Okay. Thanks.

Next up is Robert Soiffer.

DR. SOIFFER: Thanks very much for giving me the opportunity to speak today. I actually am not going to speak with slides, just from notes.

I represent the American Society of Blood and Marrow Transplantation. I have the honor this year to be the President of that society. I have nothing to disclose regarding this presentation.

As President of the ASBMT, we represent approximately 1,400 to 1,500 members at 300 transplant centers in the United States and their patients. And I think all of our members, as well as everybody in

this room, agrees that the objective of paramount importance is for us to provide or have available safe and effective cellular products for all of our patients who need them.

As you probably know, last year in the United States there were close to 4,000 patients who underwent an allogeneic transplant of some sort from an HLA identical or mismatched family member. Unfortunately, only 25 to 30 percent of the patients have donors in their family who can serve or have relatives in their family who can serve as donors.

And over the past 15 to 20 years, unrelated donor transplantation has allowed many of these patients without available family members to undergo successful transplantation for their malignancy or their genetic disorder.

Still, despite the generosity of these marvelous volunteer donors as well as the efforts of programs like the NMDP, many patients are still unable to find suitably matched donors for their particular disease. This has been particularly difficult for ethnic minorities, notably African Americans, in the

United States.

The availability of cord blood units has dramatically helped fill this unmet need. And as we heard from Dr. Rubinstein, initially cord blood was used. It was applied in pediatric populations. But now it is being used for adult patients. And as we just heard, 20 percent of those cords are coming from outside the United States.

Large registry data from Dr. Rubinstein and the IBMTR, as well as from Eurocord, published in 2004 demonstrated -- and Dr. Rubinstein showed some of this data -- the results of cord blood transplantation and showed that they closely approximated in many cases those of matched, unrelated volunteer donor transplant. Some centers think that cord blood transplant should be used actually in preference to matched unrelated donor transplants.

Now what Dr. Rubinstein pointed out, and what is very important for everyone to keep in mind, that the analysis of our data -- of the data to date -- suggests that the two most important factors that impact on survival of patients -- life and death for

patients, are the cell dose that is given to patients as well as the HLA matching.

And despite some questions here and there, there is no evidence to date which informs us that a specific manner of collection, processing, storage, et cetera, of cord blood definitively has a negative or positive effect on patient outcome.

Now as all of you are aware, the recently passed U.S. Stem Cell Therapeutic and Research Act from HRSA requires reporting of the results of all stem cell or allo transplants, including cord blood. And as these data become compiled nationally through the CIBMTR and analyzed, we'll likely gain more insight into the consequences of different processing methods as well as the different transplant methods associated with cord blood transplantation.

Now you'll hear in a couple of seconds from NetCord and FACT that they have and are establishing professionally-recognized standards in transplantation for cord blood processing and are in the process of accrediting and have accredited cord blood banks. You'll hear about this, as I said, in a

second.

Getting back to a patient in choosing an appropriate cord unit, the physician who has the responsibility to do that certainly may use and should use accreditation by FACT and NetCord as an important factor in choosing a particular unit.

But -- and this is a very, very important but -- it would be inappropriate, extremely inappropriate to pass over units with optimal cell dose or better HLA matching solely on the basis that it came from a particular bank that was not accredited or licensed or from units obtained before standards were implemented as we just heard.

We really feel that this practice would put the patient at risk and would compromise their survival. This may be particularly true for banks outside of North America and Europe and could pose additional problems for patients of non-Western European descent.

So in summary, I'd like to say that on behalf of ASBMT that we believe that licensure of cord blood banks should not limit access to cord blood

units collected at banks without licensure or prior to licensure because the unintended consequences could be catastrophic for many patients. Certainly a degree of regulation of cord blood banks is appropriate in the future and we urge the Agency to continue watchful waiting to evaluate how the therapy evolves under the current system, the clinical judgment by the physician and the standards and accreditation by FACT and NetCord.

We urge caution in establishing licensure requirements that would prohibit and prevent the use of optimal cord blood units for patients. And if such a plan is implemented, it should be done so in carefully measured steps.

Thank you.

CHAIR MULÉ: Thank you.

Next up is Phyllis Warkentin.

DR. WARKENTIN: Thank you for the opportunity to speak on behalf of the Foundation for the Accreditation of Cellular Therapy. I have, unfortunately, no financial gain from this talk today and have no disclosures.

The compliance with internationally accepted standards for cord blood banking is an important measure to ensure that high quality, appropriately tested, and matched cord blood units are available to patients who need them.

And this is for the reasons that we've heard about all morning. There are many units in inventory. Import and export is very important and needs to continue so that patients have proper access. And governmental regulation varies from country to country so it makes it very difficult for cord blood banks who send units to many countries to comply with all of the various regulations.

Comprehensive professional standards and a rigorous voluntary accreditation program have been developed and implemented internationally since 2000 by the International NetCord Foundation and FACT, the Foundation for the Accreditation of Cellular Therapy.

The goals of these cord blood banking standards and associated accreditation program are to promote quality practices in maternal and donor selection, screening, and testing. And in cord blood

collection, processing, testing, banking, selection, release, and transport to consistently assure the worldwide provision of quality cord blood units for transplantation to patients who could potentially benefit and to permit the continuation of important research and development in the area.

As you may know, FACT was founded in 1996 by the American Association for Blood and Marrow Transplant and the International Society for Cellular Therapy to establish standards for quality medical and laboratory practice and to implement a voluntary inspection and accreditation program in hematopoietic cell therapy.

Recognizing the critical importance of international standards, FACT has also worked with JACIE, the Joint Accreditation Committee of the EBMT, European Group for Blood and Marrow Transplantation, and ISCT to develop and implement joint international standards and programs for accreditation.

These cellular therapy standards apply to hematopoietic progenitor cells and to therapeutic cells from any tissue source and cover all phases of

collection, processing, and administration. All accredited clinical collection and laboratory facilities are required to develop and maintain a comprehensive quality management plan, to evaluate and report clinical outcomes, and to comply with applicable law.

Therefore, FACT is familiar to and has earned the confidence of the clinicians who will be transplanting cord blood cells. A total of 248 hematopoietic cell transplant programs in the United States, Canada, and Australia have applied for FACT accreditation. Of these, 151 programs have been accredited, representing approximately 92 percent of the hematopoietic cell transplant programs in North America.

In Europe, there are currently 36 transplant programs in 13 countries accredited under the identical standards by JACIE.

NetCord-FACT international standards for cord blood processing, testing, banking, selection, and release were developed by experienced professionals in cord blood banking and

transplantation from ten countries and first published in 2000. The third edition of cord blood standards, published in 2006, is available on the FACT website and a copy has been provided to each of the Committee members today.

These standards are designed to promote quality throughout all operations of the cord blood bank that will lead to consistent production of the highest quality cord blood units.

NetCord-FACT standards cover all phases of cord blood collection, processing, testing, banking, selection, release, and transport. An accredited bank must maintain a comprehensive quality management plan that addresses most, if not all, of the applicable governmental regulations both in the U.S. and in the European Union.

The quality management requirements delineated in NetCord-FACT standards include a defined organizational structure with a Director, Medical Director, Quality Management Supervisor, and collection laboratory staff whose training, experience, and competencies for these tasks are all

described.

The Quality Management Supervisor is responsible for establishing and maintaining systems to review, modify, approve, and implement all standard operating procedures, and to monitor compliance with standards and applicable law, including the detection, documentation, evaluation, and reporting of errors, accidents, biological product deviations, adverse events, variances, and complaints.

The quality management plan requires written process control procedures to ensure that products conform to specifications, are correctly identified with a unique numeric or alphanumeric identifier, are not contaminated or cross-contaminated, and that they maintain functions and integrity.

Standards require monitoring of clinical outcomes, maintenance of appropriate, safe, and secure facilities, detailed records, and documented agreements with other facilities participating in the processes.

Comprehensive, detailed operational

standards also cover all phases of the cord blood banking operation, including donor screening and testing to determine eligibility, maintenance of written standard operating procedures and the validation and/or qualification of equipment, supplies, reagents, and procedures.

Labeling must include bar coding or equivalent human and machine-readable procedures for maternal samples, the cord blood unit, the cord blood unit reference samples, and associated documents. Terminology consistent with the ISBT 128 is used as this terminology and labeling system are internationally understood and applicable.

Specific tests are also delineated to measure the purity and potency of each unit. Other activities in the cord blood bank are also covered such as transfer of an inventory to another bank, temporary cessation of functions or the management of units that were collected, processed, or tested using methods and/or criteria different from current protocols.

The FACT-NetCord accreditation program is

based completely upon the standards that we have just discussed. The process is voluntary and is based on documented compliance with all applicable standards.

The accreditation includes both an onsite inspection and the submission of written materials. There must be a process to address each standard as there is no partial accreditation available under this system.

Volunteer inspectors are all highly qualified and experienced in the field of cord blood banking or transplantation and are affiliated with applicant or accredited banks.

The onsite inspection is a rigorous process involving two full days during which time the cord blood collections and processing events are observed at all laboratories, all collection sites, up to five, and if applicable, at a percentage of the additional collection sites.

The inspection team report is reviewed by experienced staff and presented to an expert cord blood accreditation Committee for review and a decision regarding the next steps.

All deficiencies must be corrected prior to accreditation and thus we believe that the process is consistent from bank to bank. And the resulting accreditation indicates compliance with all standards.

There are 54 cord blood banks who have applied for FACT-NetCord accreditation. Thirteen, to date, have been accredited. The remaining 41 are in the accreditation process at some point with six of them having completed the onsite inspection.

NetCord-FACT standards have achieved international acceptance in cord blood banking. The 13 accredited banks represent nine countries. The standards have been translated into Italian, published in Italy for clinical guidance, and accepted by the Italian Ministry of Health as recommended practice.

In Australia, the Therapeutic Goods Administration, Office of Devices, Blood, and Tissues regulates cord blood under the Australian Code of GMP and the NetCord-FACT standards.

The World Marrow Donor Association and the AsiaCord have also adopted NetCord-FACT standards.

This slide lists the 13 accredited banks.

As you can see, they represent nine different countries, including four banks in the United States.

In summary, comprehensive, internationally developed and accepted voluntary standards for cord blood collection and banking have been in place for five years encompassing comprehensive quality management process controls and evaluation of clinical outcomes.

During this time, considerable experience has also been achieved in a rigorous inspection and accreditation process for cord blood banks. Professional accreditation should be considered as an important measure of quality of the cord blood bank and of the units manufactured therein.

Import and export of cord blood units is critical to the care of patients whose most appropriate cellular therapy product might have been collected in another country or using alternative processing methods or acceptance criteria.

As established by FACT and NetCord, the accredited cord blood bank must have controlled processes that will ensure safety, purity, potency,

and identity of the cord blood units.

Thank you.

CHAIR MULÉ: Thank you.

Bill, you had a question?

MEMBER TOMFORD: Have there been any reports of transmitted disease in cord blood?

DR. WARKENTIN: They wouldn't have reported them to me, but I'm not aware of any. But maybe I should ask somebody else probably to answer that.

Pablo?

DR. RUBINSTEIN: I am not aware that any products have transmitted infectious disease. But there have been a few cases in which leukemia has appeared in the recipient and was tracked down to the donor as the origin.

It is a fascinating topic. There are very few cases compared to the total number of transplants but it is a most interesting development. And one that should be studied.

MEMBER KURTZBERG: Could I just clarify that statement? The leukemia was in donor cells. The

donor themselves did not have leukemia. You know, in other words, the recurrence of leukemia in -- I'm aware of two patients with leukemia to begin with was in donor cells. But the donor, themselves, did not have leukemia.

DR. RUBINSTEIN: Yes. I fully agree with that correction. It is not a transplant of the leukemia but rather it is the emergence of leukemia in cells from the donor. And there are, I believe, in addition to the early two cases in the -- one in the United States and one in Europe, there are now two cases in Japan.

CHAIR MULÉ: Mary?

MEMBER HOROWITZ: And consistent with our charge today, there have been no reports of things that you might have screened for that have been transmitted to recipients, you know, suggesting that perhaps screening procedures were inadequate in some banks.

DR. RUBINSTEIN: Yes, no, no. It is an entirely different process. The work of Dr. Greaves, Michael Greaves in London, probably contains at least

a major part of the explanation for this phenomenon.

CHAIR MULÉ: For the sake of time, we will have to move on. Folks have planes to catch at three o'clock or so. So we're on a tight schedule. And we'll probably tackle some of these questions in the afternoon session.

Next up is E. J. Shpall.

DR. SHPALL: Yes. Thank you very much for the opportunity to speak to you today representing NetCord, if we can find the slides here. As I said, I'm representing NetCord today. That is an organization that has been in existence for more than a decade. We are newly elected officers.

Actually Pablo Rubinstein was the Vice President. And it is he and Peter Wernet and the originators who are actually solely responsible for getting NetCord organized and into what is a very important and global body of cord blood banks.

As you can see here, the banks that are -- there are 22 banks now represented in NetCord. Only two banks in the United States, Pablo's bank and one in Houston. The rest involve cord blood banks in

Australia, Europe, Israel, and Asia in Tokyo with far-reaching implications for the patients.

The inventory, you can see here, is 137,820 units. As of a year ago in the BMDW, I think the worldwide inventory of listed cord blood units was about 258,000. So this is a fairly substantial percentage of the units that are out there available to our patients.

And as I showed you, we've distributed many units throughout the world -- NetCord has to various countries. You can see 78 in the United States but they are providing units -- that the major user is in Europe but also elsewhere as shown here -- Asia and Australia.

And as you heard from the previous speaker, in calendar year `05, the World Marrow Donor Association calculated that approximately 16 percent of units were imported to the United States from banks outside our country. In `06, that was 19 percent. And in their most recent calculations, they are estimating that 20 percent of the units last year came into the United States from outside our country.

Based on this as well as the NMDP records, this figure is likely to grow because definitely each month the number of cord blood units being moved is increasing.

As you just heard from Phyllis Warkentin, there are professionally recognized international standards with rigorous onsite inspections that are looking at the quality of these units outside the United States. And we think go a long way to protecting our patients.

And we wanted to echo Dr. Soiffer's comments. We applaud the FDA and we agree with them that it is critical to move the quality of the units that are coming in to our patients up. But we are just cautious about preventing options for patients who otherwise will definitely die of their disease. The selection of cord blood units today is clearly the practice of medicine.

Our patients, particularly in some of the larger urban centers where we have big transplant centers, are ethnically diverse. Often the best unit for our patient is in another country. And denying

access to such units would primarily effect these minority patients for whom cord blood is often the only therapeutic option.

Our concern is that there is no reason to assume that the current inventory is not safe. We haven't heard of any major catastrophes in terms of infectious disease transmission. And so we think that patients must have access. We need to work with the FDA to make sure that the existing inventory, both old and outside this country, can be used.

One of our concerns is that if a license is required and the procedure to then obtain a non-licensed unit under the clinical need or medical necessity is too burdensome for busy clinicians who are doing a million things every day when they are consenting these patients would be -- that the path of least resistance would be to perhaps choose a unit where the burden wasn't there. So that at least the patient could get transplanted.

And in the end, that will not be a service when we know this is such a critical patient population where every little aspect of care can make

the big difference between survival and not.

In terms of one of the major guidance document issues, which is the CLIA certification, that clearly represents a problem for places outside the United States. There aren't many CLIA-certified laboratories in Europe. In fact, only one at the moment that we know of. So we were hoping to engage -- NetCord is hoping to engage the FDA in a dialogue, perhaps acknowledging comparable certifications from other countries that might meet the CLIA certifications.

Another option would be to take these units that would be shipped into our country and test them right before release in a CLIA-certified laboratory rather than prevent their use altogether. And we're hoping that NetCord can work with FDA to assure the access of their high quality units into the United States patients as this moves forward.

And we'll end by echoing the ASBMT comment that clearly the risk to be prevented with licensure is undefined although we applaud the ability to raise the quality. But the risk of denying access to the

most appropriately matched units of cord blood is clearly defined in our patients.

And we thank you for your attention.

CHAIR MULÉ: Thank you.

Next up is Elizabeth Read.

DR. READ: Good morning. I think it is still morning. My name is Elizabeth Read and I am representing the International Society for Cellular Therapy, or ISCT. And I have no financial conflicts of interest to disclose.

ISCT is the global forum and resource for developing and supporting innovative cellular therapies through communication, education, and training, thus furthering clinical-based investigation for the benefit of patients.

ISCT appreciates FDA's thoughtful and flexible approach to licensure of allogeneic, unrelated cord blood. ISCT members and leadership have reviewed the document and participated in the work group consisting of AABB, ISCT, and the National Marrow Donor Program. And that work group will be submitting written comments to the docket.

Today's comments are general concerns aimed at raising questions, promoting clarification, and stimulating further discussion. We believe the most critical issues raised by this guidance relate to three areas; the first, product potency; the second, product comparability; and the third, the impact on the practice of medicine.

And I think you've heard all the previous speakers touch on all of these areas. So what I'm saying is not going to be new, but I may be framing it just slightly differently.

With regard to product potency, Dr. Lazarus mentioned the recommended testing for product potency that appear in the guidance on pages 8 and 35. And that is the total nucleated cell content of greater than or equal to five times ten to the eighth per unit, the viability of the nucleated cells, greater than or equal to 85 percent after volume reduction and before cryopreservation, and a viable CD34+ cell content of greater than 1.25 times ten to the sixth per unit, also after volume reduction and before cryopreservation. And that value is achieved

if the minimum specified total nucleated cell content has at least .25 percent viable CD34 cells.

These recommendations are all reasonable, but we'd like to discuss a couple of issues related to product potency and raise the following questions.

I guess the first issue is that there is a real challenge in selecting a product potency assay or a set of assays for cord blood. Several issues arise.

This guidance is focused on banking for specified indications for which current data are available. But the reality is -- and this has been mentioned by other speakers -- that public cord blood units are, and will be, banked for a variety of current and future indications.

For example, with increasing use of non-myeloablative transplants, we do not really know whether potency assays should be based simply on the content of viable CD34 cells, immune cells, some combination, or something else to be defined after further clinical trials.

Dr. Rubinstein also mentioned the use of

double cord blood transplants and that is increasing in the transplant world. And that changes the way we view product dosing, which is related to -- which does have a relationship to product potency.

Finally, we need to consider other potential uses of cord blood, such as cardiac and skeletal repair. And there are many others as well in the future that we may not even have thought of yet which may not be dependent on hematopoietic progenitors.

Just to hone in on one issue that relates to use of viable CD34 cells, there are reasons why the number of viable CD34 cells as a single assay may not be the ideal potency assay even for specified indications. Published data in literature show that TNC has actually been the best predictor of clinical outcome and transplant physicians typically use the TNC before the CD34 cell dose in the unit selection process.

And the reason for this is most likely related to the fact that many units never had CD34 measured. And even those that did, CD34 quantitation

of cord blood is not as well standardized as for bone marrow PBSC and thus is subject to greater inter-laboratory variability.

So the use of one single potency assay that is in a particular guidance may not be the solution to approaching the potency issue.

It is our understanding that FDA will require each bank to specify a potency assay or assays for its own use but that they are not defining exactly what the assay or assays must be. And we strongly support this approach but also encourage banks, transplant centers, the FDA, and other parties to continue thinking very broadly about this issue and to collaborate actively to identify the most appropriate potency assays for specified clinical uses of cord blood.

So the second issue is product comparability. And establishing comparability of units in pre-BLA inventory is perhaps the most critical and challenging issue. Criteria for comparability, in fact, encompass the entire manufacturing process, including donor eligibility, ex

vivo processing, storage, final product specifications, labeling and expiration dating, and CGMP practices and facility requirements.

There are a number of concerns of both cord blood banks and transplant physicians with regard to product comparability. And, again, you've heard these before. The post-BLA units may be perceived as better by whatever parties than pre-BLA units. Valuable inventory would possibly need to be discarded.

The nature of the BLA process will result likely in proprietary communications between individual banks and the FDA on this issue. And the use of comparability standards will impact the availability and use of cord blood units collected by non-U.S. banks that are not FDA licensed.

So we strongly support collaborative efforts among banks, professional organizations, and FDA to establish industry standards for product comparability. And I think this is going to be an extremely challenging process. And I'm sure the Committee will be talking a lot about this specific

issue this afternoon.

Finally, the practice of medicine. Cord blood transplantation is often the last resort for patients with life-threatening illnesses. And transplant physicians do need latitude in electing to use cord blood units that may not meet BLA specifications after weighing the appropriate risks and benefits.

We request that the FDA consider and clarify its position and provide additional comments -- and actually this isn't just the FDA -- it's the Advisory Committee that we're asking for this as well -- provide additional comments on and options for continued storage of cord blood units that do not meet a licensed banks prospective or comparability specifications for clinical use and options for clinical use of cord blood units for indications other than transplantation of hematologic malignancies.

ISCT thanks you for considering these issues. And thank you for your attention.

CHAIR MULÉ: Thank you.

So I'd like to thank all the speakers who

participated in the open hearing.

And what we will do now is break for lunch and plan to reconvene at 12:45. Thank you.

MS. DAPOLITO: And there is a reserved section in the restaurant for the Committee so you can get back in 45 minutes.

(Whereupon, the foregoing matter went off the record at 11:59 a.m. to be reconvened in the afternoon.)

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

12:50 p.m.

CHAIR MULÉ: Okay. So in order to keep on time, mainly for individuals who need to catch flights, we have four questions that FDA has asked us, as a Committee, to provide comment on. And so we have roughly two hours to do this.

And so what I'd like to do is have the Committee members make comments specifically to each of these questions. And then, if time permits, we can open up for comments from the audience. We'll see how it goes. Okay?

So will we flash up the first slide? The first question -- do we have a first question? So without reading the entire question, I'd like to open up the floor to members to comment.

MEMBER GERSON: May I?

CHAIR MULÉ: Okay, go ahead.

MEMBER GERSON: So it does seem to me that the issue of how to come up with the question of potency, which it looks to me like is the major focus of this question, can be addressed with cell number

viability, CD34, and colony-forming unit.

There is enough variability between those assays that other than cell number, neither is more accurate than the other. And so they give you a cumulative -- a valuable cumulative sense of potency.

The bigger issue to me, and I'm curious about others' perspectives, is the restriction in this question to previously manufactured and currently manufactured whereas we've heard from the folks who came and spoke to us about another major concern and that is availability of internationally-based samples that may or may not be previously or currently manufactured.

So I think there are two components here but they both relate to this issue of potency. And all of these components, I think, are reasonable measures of potency.

MEMBER HOROWITZ: I guess the question is do we need all of them or any one of them? In all the clinical studies, the consistent piece of information about the graft that has been most convincingly shown to correlate with outcome is the total nucleated cell

dose.

And I think it is hard to argue that any of the other things are absolutely superior to total nucleated cell dose in demonstrating the adequacy of a unit. There are certainly studies that show that CD34 correlates. But I don't know if it is convincingly demonstrated to be so much better than total nucleated cell dose that it should be required.

Joanne, I'd be interested.

MEMBER KURTZBERG: One of the problems with requiring this now, although I think they all have value, is that there is not standardization between the methodologies used or the results obtained from bank to bank. And there have been some efforts made through Stem Cell Technologies and their QA program through the NMDP and some of the European banks to try to standardize the assays so that everybody measuring the same sample would get the same result.

And it is very easy to do for TNC and viability and the correlations are good. But when you move to 34, it is okay, not great. And when you move

to CFUs, it is horrible. And that is despite quite a few efforts. And it is not just in cord blood that standardizing CFU has been a problem.

Fifteen years ago, the T cell depletion trial, which was a marrow trial, tried to do the same thing with workshops, et cetera, and still had problems.

So I think the reality is that requiring it now is almost like it is not ready for prime time because of these deficits in the technologies. But in the long run, these may be good assays to have information about.

If you look in individual banks or individual inventories, you do see correlations of both 34 and CFU with engraftment and survival. But when you try to cross broad numbers of inventories, then you lose the significance. And I think it is a technical thing.

I will say one other thing, though. I think that a test of potency or viability -- I'm not even sure what you want to call it -- is important. And I think the CFU does that. The drawback to the

CFU is that it takes 16 days. So to use it as a real time release assay or to use it as a real time potency assay in the setting of a transplant isn't very practical.

CHAIR MULÉ: Doris?

MEMBER TAYLOR: I just wanted to make the point that discussing potency when we haven't completely discussed all the indications that the two may be closely related.

And that if we broaden the indications, we may end up wanting to change some of the potency assays as well, especially if we move outside hematologic disorders or if we don't have a good sense that CD34, for example, correlates with potency in some of these other indications.

CHAIR MULÉ: Mary?

MEMBER LAUGHLIN: I agree. And even within the context of hematology applications, potency assays focused on the immune cell component of the grafts have really not been studied to determine whether they would be predictive of engraftment or transplant outcomes.

CHAIR MULÉ: Dr. Horowitz?

MEMBER HOROWITZ: If we're talking about homologous use here, not about the use of these cells for regenerative medicine, for example, then I think it doesn't really matter so much in terms of the underlying indications.

The homologous use for hematopoietic reconstitution in the context of a transplant, I don't think it matters too much whether we're talking about malignant disease or nonmalignant disease. You probably have some variation depending on whether you are talking about myeloablative or non-myeloablative conditioning although actually we don't really know that.

The double versus single cord blood, in terms of establishing thresholds for cell dose, might make a difference. But in terms of just saying what tests would you do, I think you can still say that the thing that is the most reproducible, that has the strongest correlation with all the important outcomes in all the clinical studies that have had enough size to be worth looking at is total nucleated cell dose.

So I think that total nucleated cell dose is sort of the main thing that has to be looked at. It definitely is a predictive variable for outcome of these transplants.

CHAIR MULÉ: You know when it said the types of data that could be submitted to demonstrate comparability between the previously manufactured cells and the cells manufactured currently, how would that be done? How would that comparability be done? I mean we're talking probably about different processes. And I'm not sure how --

MEMBER HOROWITZ: I don't even really know what comparability means in this context. It's not like a drug where you want the same dose in every drug. I mean that's just not the nature of the product that we are talking about here. Every product has a different cell dose that is sort of dictated by the person -- the cord from which the cells are collected. And that's the total dose.

And then the cell dose is, you know, totally dependent on the size of the person you are putting it in. It's not like you can adjust your cord

blood.

So I think comparability then defaults to clinical grounds that among cord bloods done for similar indications with similar cell doses, you get the same rates of engraftment. I don't know. I think that is the only way you can talk about comparability.

CHAIR MULÉ: Donna, did you want to comment?

MEMBER REGAN: I believe from a cord blood bank point of view, that comparability could be measured by stability studies which are already required by accrediting agencies. And you take not only the characteristics of the products that you have in the bank over time but then you can relate that to those that have been transplanted within those years and look at the outcomes.

So you have not only the stability of the product per temperature and length of time but then you would also have some of those units that were transplanted that you could compare those characteristics to.

And in the end, using the same

specifications that you used up front with your preprocessing, with your postprocessing, your segment studies, and then the clinical data would be the way that I would address that issue.

CHAIR MULÉ: Joanne?

MEMBER KURTZBERG: I think you could create exercises within your laboratory where you periodically took units by your old method and your new method and, you know, you split a big unit, processed it both ways, and then compared recovery post-thaw -- post-processing and post-thaw of these things -- CFU, CD34, sterility, viability, TNC.

And if you could show you got the same numbers on the same unit doing it both ways -- and, of course, you wouldn't do just one unit. You'd have to do some number. I think that that would, in addition to the clinical data that you already have that these older units have been engrafting and doing well and meet the kind of standards that have been reported, that that is the best you are going to do.

CHAIR MULÉ: Dr. McCullough?

MEMBER McCULLOUGH: Yes, I think Donna and

Joanne have said nicely how comparability data could be obtained that would make sense in relation to what the bank is currently doing.

I have two very specific comments. One is the terminology of, if CD34 cells are included, that the terminology of viable CD34 cells -- and as a number of people here know, a lot of the older ways of determining viable CD34 cells had to do with just quantitating CD34 and doing total nucleated cell viability. And then multiplying as opposed to in FACT system actually looking at viable CD34 cells.

And a lot of the old units in the banks will have been -- the viable CD34 content will have been determined by that old method. And it might not be that accurate depending on the number of granulocytes and other kinds of cells that were in the product.

So one issue would be whether you really mean viable CD34 cells or whether those other methods could be used. Because it could turn out to be a real problem for some of the older units.

And actually while I'm on, let me just

mention progenitor cells as well. As has been pointed out, the ability to relate a number in the progenitor cells assay to transplant outcome isn't a very good predictor. On the other hand, it would seem to me as a general form of quality for putting cells into a bank, the progenitor assay can be looked at almost as an all or none phenomenon.

That if we had a unit that didn't grow in a progenitor assay, we would want to take a very close look at that unit to determine whether or not we really wanted to bank it because often there will be other things wrong with it. It will have a low CD34 count or other things like that.

So I'm not so negative on the progenitor assay as maybe others if you think of it more as a broad, almost an all or none kind of thing rather than trying to get a particular number that relates to a likelihood of engraftment.

CHAIR MULÉ: Donna?

MEMBER REGAN: I just have a follow-up comment to Dr. McCullough's. The number that we would get on CD34 of the older units that was assayed by his

description could actually be more conservative than what it is we are doing now on flow cytometry by gating the viable cells first and then getting CD34. So it was just a comment that that could be a more conservative number actually, which is better than having it the other way around.

CHAIR MULÉ: Michéle?

MEMBER CALOS: I have a question for the non-hemotologists. When a transplant doesn't succeed, is that due to the cells you are transplanting or to the recipient? You know, can you give us a sense of that?

MEMBER HOROWITZ: The major drivers of success after hematopoietic stem cell transplant of any cause are transplant-related mortality and recurrence of the underlying disease. And they actually account for about equal proportions of the deaths.

Most of the transplant-related deaths are not due to failure of the graft to engraft but to organ toxicity and graft-versus-host disease. So I would say that failure of a transplant to engraft is

not a frequent cause of failure in general.

There are some cord blood transplants with low cell doses and high degrees of mismatch where it becomes a significant cause of treatment failure. That's not because that cord blood unit is of poor quality, per se, but perhaps was the wrong choice, you know. So that unit may have been just fine for a smaller patient with a different HLA type. So it is not something where you would -- it is anything about the manufacture. But the cell dose and the HLA match can influence that likelihood.

CHAIR MULÉ: Joanne, you have a slide?

MEMBER KURTZBERG: I just wanted to show one slide to show how it can be useful. These are CFUs. These are transplants at Duke in 160 children with metabolic disorders. Looking at survival as a factor of recovered CFU and the thawed product infused per kilo.

And you can see that there is a very nice break between kids who get more than 5.6 at this point times ten to the fourth CD34s per kilo. I'm not sure the number matters. But it's just in a laboratory

that does it all the time -- and these are not all Duke units -- these are units from banks all over the place -- we can actually see a very nice correlation with CFUs.

MEMBER HOROWITZ: But can't you see that with TNC also?

MEMBER KURTZBERG: No, it doesn't break. You want to see the TNC? The TNC is right there. It's not nearly as clear cut.

MEMBER HOROWITZ: Well, I have some slides, too, I can show you that I show a nice separation with TNC.

MEMBER KURTZBERG: Yes. But this is the same dataset, same patients, same product, same numbers. That's the TNC infused. I have the 34 infused. And then I have the CFUs infused.

MEMBER HOROWITZ: There's a threshold.

MEMBER KURTZBERG: There is. But I'm just saying in this -- you know, in a lab that does it the same way every time, not necessarily the right way but a way, and I have the same Russian lady ready CFUs for 20 years truly, we get a very nice correlation. And

that's the best correlation. And that's on the infused product, not the cryopreserved product. So it is post-thaw.

MEMBER HOROWITZ: Other than the cobalt study, which had multiple centers.

MEMBER KURTZBERG: Cobalt didn't look at CFU. Cobalt looked at 34 which did not correlate and they only looked at it on the cryopreserved product. And TNC, which did correlate.

CHAIR MULÉ: Dr. Rubinstein?

DR. RUBINSTEIN: We have had an opportunity to look at these years ago in collaboration with Dr. Mitchell. In that study, we had compared the CFUs with total nucleated cells in over 600 transplants. And the results were very clear cut in that the coefficient of correlation with the CFUs was slightly better. Not very much better but it was slightly better than with the TNC.

So while on the one hand we were disappointed because it is so much work and the improvement was so little, on the other hand, it was consistent with the idea that CFUs represent a form of

cells that is more closely associated with engraftment. So that study was part of another study reported in Blood in 2002. Thank you.

CHAIR MULÉ: Thank you.

Stan?

MEMBER GERSON: Try and look at the rest of this question, if we could, so we focused on the cell count, CD34 and colony. Other parts of the question speak to product attributes, giving us all the leeway we want here.

Obtained from stability and other studies, data cited from the medical literature, and clinical outcome data -- I don't know how in the world to relate those latter elements to issues of comparability. And I would suggest that we stick to numerical data.

CHAIR MULÉ: Comments about that?

MEMBER HOROWITZ: So I can understand looking at pre-thaw, post-thaw types of measurements, you know, in one era versus another era or with one method of processing versus another method of processing to say, well, you get the same results.

It's the same -- when you thaw the unit, you have the same recovery on a variety of parameters, whether you're talking about TNC or CD34 or CFU.

And if that is all we're talking about, that is certainly a numerical thing. And if we say that as long as you can show that the product is equally stable, it's fine, that's fine, too.

The only thing that matters -- none of these things are perfect in predicting engraftment. And so I don't know -- you know other than stability in the pre- versus post-thaw, I don't know how you would go about proving comparability of units obtained in one -- obtained and processed in one way versus units obtained and processed another way without looking at some kind of engraftment parameter. You can't look at the cell doses. That's not helpful.

CHAIR MULÉ: Mary?

MEMBER LAUGHLIN: You know as a clinician, certainly that which Dr. Gerson brings forward is important in that in analyzing the product pre-freeze, post-thaw, you know, in numerical data in assessing a product, the ultimate potency assay is whether or not

that product engrafts in the patient.

And the challenge there is the numbers of factors that influence that engraftment in the human being. The stage of their disease, whether they have an infection post-transplant, the type of conditioning that they received. There are so many confounding factors that to try to utilize that as a parameter of the potency of the product is challenged by those numbers of factors.

The additional comment that I would make is my knowledge of the struggle under current INDs by the cord blood banks to obtain this valuable information from the transplant centers as they are required under their INDs, I think it is going to be important for the Agency to look carefully at the accountability of the transplant programs within the context of these guidance documents.

MEMBER HOROWITZ: Well, I can comment on that because with the legislation of 2005, it will be mandatory for all transplant centers to provide outcome data on all allogeneic transplants regardless of the product used in the U.S.

So in the U.S. there's now the force of legislation and we've been working very hard to figure out what data on the cord blood grafts and recipients we need, to be able to make those assessments. And that program of collecting those data on all U.S. recipients should be launched in July of this year.

We're also working with EuroCord and the Japanese Transplant Society to collect the same data on the outcome of transplants using cords that are collected in the U.S. but going elsewhere. And we hope that will be in place in about a year.

CHAIR MULÉ: Donna?

MEMBER REGAN: Thank you, Dr. Laughlin, for recognizing the challenge that we have without outcome data. And while going forward transplant centers are going to be more accountable for giving us that data, there are thousands of transplants that have already been done for which retrospective data may not be available either because of loss of contact with the patient or, in the European data, NMDP hasn't been collecting that data from Europe.

And so, you know, there wasn't that

agreement until now. And it is being worked on very nicely. But we do have thousands of transplants that it might be difficult to do some comparability with because of that. So we're doing the best we can with the data that we have. And thank you for bringing that out.

CHAIR MULÉ: Joanne?

MEMBER KURTZBERG: I was just going to say that while I agree with Mary that the true potency assay is the engraftment after transplant, that is a retrospective analysis. And I think probably what needs to be put in place through the SCTOD is a way to look back on a periodic basis as a quality measure to see if there are any red flags coming up either by bank, by transplant center, by disease, by parameter of dosing that says, "Uh-oh, we've identified a hot spot that we need to take a look at."

It's almost like having stopping rules without having a protocol. And I think maybe that can be put in place.

CHAIR MULÉ: Dr. McCullough?

MEMBER McCULLOUGH: These are -- if you

want me to wait, these are more general comments that apply to the concept of licensure and what we're doing here that's going to -- based on several years experience we have. So whenever you want --

CHAIR MULÉ: Okay, we'll come back to you.

Mary, do you want to respond?

MEMBER HOROWITZ: Maybe those comments are what I'm looking for because what I'm thinking as a transplant physician in terms of if there is a bank that has been doing things not as outlined in the guidelines but has provided a lot of units and has outcome data that says these units work as we would expect them to, then I don't care so much what any of the other studies show.

I'm not saying that you would have to have outcome data. I'm saying that outcome data would be very -- is the ultimate. And would be very convincing to me as a transplant physician that, however these units were processed, they are quality units that do what we want them to do.

And that's why -- I'm not saying we have to have outcome data but I think outcome data, if

available for a procedure that is somewhat different than in the guidelines, would be convincing to me.

CHAIR MULÉ: Go ahead.

MEMBER McCULLOUGH: That is kind of what I was going to say. A number of you know this. We published a couple of years ago looking at -- this is going to take about three minutes or so. It is a paper we published.

Looking at it from the transplant center, we scrutinized about 300 units of cord blood that were sent in to us for transplantation over about a two-and-a-half year period. And these came from banks in the United States and in Europe.

Essentially every one of those units had one or more what we would consider quality defects in it. Some of these were very minor but some were major. And they ranged from things like positive bacterial cultures, transmissible disease testing on donors not complete, accompanying paperwork that did not have the unique identifying number on it so you couldn't be sure that that document actually had information on it that related to the unit that we

received, some sort of things like this that most of us familiar with quality would consider pretty onerous problems.

From what little I know about the FDA one of their reactions would be that this represents institutions that are sort of out of control -- I think might be an FDA inspector's term for this. One of the problems with this is that usually we didn't find out about this until the decision to transplant had been made. These were units that were selected for transplant and they were shipped to us within maybe two weeks of the time of transplant.

So we had to scramble around and do a lot of communicating with the banks to try to sort out whether or not to use those units. But to get to your point, Mary, virtually all of them -- I think actually all of them were used and there wasn't any evidence that those units performed any better or any worse than other units that we had received at different times.

And so I'm sort of left with a dilemma that on the one hand I do agree that these are things

that indicate to me that these banks weren't operating the way you would like to see them operate under these draft guidelines.

On the other hand, we only encountered one unit where there was a disastrous problem and it was a failure to engraft. And that unit came from -- it was the first unit we received from a bank that processed the cord blood differently than Dr. Rubinstein's method but didn't tell us that. And so we used our ordinary thaw/wash method, which ended up damaging cells. And we didn't know this until too late.

So on the one hand there is ample evidence in our experience that there are a lot of things that are called for in the guidance document that banks don't do, or they don't do it the way they should. On the other hand, back to Mary's point is, to what extent does this really represent the patient safety and quality issue? And I wish I had a simple answer but I don't.

CHAIR MULÉ: Stan?

MEMBER GERSON: I'm just reminded that the

guidance document asks us to create a structure through the guidance for banks to apply for licensure. And so it is an onerous obligation on those banks if they are required to be accountable for clinical outcome data at an independent entity somewhere in the world.

So as sensitive as I am to the prior two comments because at the end of the day all that matters is, was there engraftment and was there engraftment promptly, I don't know how to enforce that as a guideline requirement.

MEMBER HOROWITZ: Yes, I would like to enforce engraftment. All units must engraft. But the concern I have is instituting guidelines so that there is some kind of quality control on the procedures of the banks so that you don't have to scramble with only two weeks left to transplant but that we don't regulate a lot of things that have not been proven to effect outcome and so impair our ability to optimize the two main things that have been definitively proven to effect outcome. And that is to choose the largest unit possible with the best HLA match.

And I think that, whatever we recommend, we have to remember that there are two graft-related things that have been definitively shown to effect outcome. And they all have to do with -- they can be optimized by having the largest number of potential units to select from in an individual patient. And without any restriction on where you go to get those units.

So we have to not do anything that will restrict international exchange of products. And, you know, the FACT-NetCord standards have tried to accommodate these things by developing a set of standards that are internationally accepted. And that would have probably just thinking about just the few examples you put forward, have addressed some of those issues in their standards.

MEMBER McCULLOUGH: The trouble is we don't want to find out the day before they are starting the preparative regimen that the unit that was sent to us has a positive bacterial culture and we didn't know it. And it really implies that the bank is not operating the way we would like to see it

operate.

MEMBER HOROWITZ: I mean those units were probably obtained before FACT-NetCord standards were implemented.

MEMBER McCULLOUGH: Well, there are only FACT-accredited banks in the U.S. at this point.

MEMBER KURTZBERG: Well, NMDP is supporting other banks to get FACT accreditation for what it is worth.

CHAIR MULÉ: Donna?

MEMBER REGAN: NMDP also has quality standards that they abide by and most of the banks in the United State, I think, are -- and CORDLINK is programmed to kick those units out presently. So you may not run across -- you probably shouldn't run across those things without knowing and having to acknowledge with a signature that you are going to take that unit.

MEMBER McCULLOUGH: Yes, well, this didn't happen that long ago. And these came from banks in the U.S. that we all work with all the time. So it's not like this is some fringe activity.

MEMBER KURTZBERG: But I think that is a good reason why we really need to standardize accreditation. We have to follow the rules we set for ourselves. And not allow ourselves to have exceptions. And have data systems that transmit the information you are talking about.

But I think that that is happening through the NMDP, through the Cord Blood Coordinating Center and it will happen through the SCTOD for outcomes data that come back to the bank.

MEMBER HOROWITZ: For the uninitiated, the SCTOD is the Stem Cell Therapeutic Outcomes Database. It is the outcomes reporting that is part of the legend.

CHAIR MULÉ: Thank you, Mary.

There is a bullet here about alternate test methods. Donna, do you want to elaborate on that. And maybe we can discuss that a bit more?

MEMBER REGAN: The alternate test methods that are out there I don't believe have been brought into the banks as they would be probably pretty unique to each bank.

There are a number of assays out there trying to determine viability by a different method. Again, we are having trouble standardizing CFU and CD34. So I'm not sure that I would go out on a limb and try and bring on any other type of assay.

I will take the opportunity here while I'm speaking to emphasize that CFU is the only functional assay that we have with these cells and I find it to be a very, very important, although laborious, expensive, and not standardized at this point, it must be considered.

Some of the data that Joanne has looked at and even if you do it qualitatively with a growth, no growth-type of issue on a segment post-thaw, it gives you some indication of the viability of that unit. And I think it is a very important test that we need to keep.

CHAIR MULÉ: Joanne?

MEMBER KURTZBERG: I just want to make one global comment really to the FDA and that is that there has been a ton of work in this community already to try to bring cord blood up to a level of

proficiency and quality. And to standardize a lot of things and to communicate and to collect data and to share data.

And I would hate to see that not really taken advantage of as the guidance is going forward and as the community goes forward.

The same is true of the indications. I mean FDA may not have approved the indications for -- or reviewed data in the docket for indications that are non-hematopoietic malignancies but there's many things published, there's lots of data there, and I don't think it would be responsible to say until we do it, it can't be done.

And I think when whatever comes into play is decided, all of the work that has been done in the community should be taken advantage of. And I think FACT is a good example of standards that are already on the table that provide a lot of quality assurance for all the things you are asking for in the guidance.

So I just want to put that across as a message because I would hate to see all the work everybody has put in not really be taken advantage of.

I think you are getting a bargain at one level, if you do that.

CHAIR MULÉ: Thank you.

Other comments? Savio?

MEMBER WOO: For a non-transplanter listening to all of this we're kind of going around in circles. And I was just wondering. We have heard presentations from the NetCord organization. There was international collaboration. We've got all of these accreditation programs. And it goes on and on and on and on.

So I was wondering are we here to reinvent the wheel? Is there something deficient in the NetCord programs? Why can't we just adopt that? And so we have an international thing to go on already. Why are we going around talking like this? Just please educate me.

CHAIR MULÉ: Is someone willing to comment?

(No response.)

CHAIR MULÉ: No comment.

Stan?

MEMBER GERSON: If I understand the good will, if you will, of FACT and the international efforts, they are voluntary. And we're here at the behest of a federal agency to establish a federal guideline that I don't believe would be voluntary.

So I believe that that is the appropriate direction, managing these other competing, very concerning issues of patient access to available products of unknown quality and the self-regulation efforts that have been done on a voluntary basis.

MEMBER WOO: My comment is not about voluntary regulatory. I'm talking about why can't the FDA adopt something like whatever is already in place. Internationally it's working. And legalize it with the same standards.

CHAIR MULÉ: And the process --

MEMBER WOO: Yes.

CHAIR MULÉ: -- and methodology.

MEMBER WOO: Yes. And the accreditation of these centers.

CHAIR MULÉ: Duly noted.

Donna, did you have a comment?

DR. LAZARUS: I'm just going to jump in with what I hope is a helpful comment that the accrediting organizations were very forthcoming with their standards. And those were submitted to the docket. And, of course, we do continue to very carefully review all those centers.

So we intended to -- we hope we achieved this -- incorporate those accrediting organization standards into our guidance document where we could link a particular standard to a regulation or a provision that would be relevant.

CHAIR MULÉ: Dr. McCullough?

MEMBER McCULLOUGH: This is -- the material about comparability really deals with laboratory testing. And it is a really a question for the FDA. There are many other parts of the guidance document that deal with GMPs and facilities and all that sort of thing.

And is the intent that units collected or being considered for comparability, that the cord blood bank would also have to show that those units met those other aspects of the guidance document?

Because, as you know, why I'm asking the question that particularly before `05 when the GTPs went into place, most banks will not be able to show that units collected were collected under the conditions that are described in the draft document. So it wouldn't even matter what kind of lab tests one did.

How do you plan to address that? It's really a question for the FDA staff, if I'm allowed to do that.

DR. LAZARUS: Well, I think that's, you know, very much one of the issues that we are glad is coming up for discussion. It's in our guidance.

It is a requirement for any licensed biological product to be manufactured in accordance with GMPs. So we start from there. And then engage in these discussions to see what the issues are pertaining to that requirement.

And we are already hearing some interesting suggestions about how these matters could be addressed. But specifically with regard to the GMPs pertaining to facilities, you know, we are very

much interested in hearing the opinions and comments from people here about important issues that we could consider in assessing that.

CHAIR MULÉ: Other comments about question one?

MEMBER HOROWITZ: Don't you think that requiring those GMP practices is going to preclude licensing of a fair number of banks?

MEMBER McCULLOUGH: That's why I'm bringing it up.

MEMBER HOROWITZ: And the question to me is, why. I mean, you know, what is that going to improve in terms of our patients' outcomes?

CHAIR MULÉ: Kurt?

DR. GUNTER: Just a comment on the question from Dr. Woo about whether we're reinventing the wheel here. You know my impression from reading the draft guidance is that the FDA is trying to be flexible. And if you've, you know, every gone through the FACT standards, they are very well written but they're very detailed and exacting.

So, you know, I don't know if it would be

a good idea to impose that on everyone that wanted to license their cord blood bank. The FDA gives latitude for validating alternative procedures.

One way might be to give a bank an option of seeking FACT accreditation which could serve as a surrogate for licensure. Or if they want to go do it their own way by validating their own procedures and justifying it to the FDA, then they would have to do that within their own BLA. So that's just one suggestion.

CHAIR MULÉ: Donna?

MEMBER REGAN: I also think we've forgotten about AABB. That also has standards in their field as well. And they should be considered.

But back to the question that you originally came up with -- and I'm not sure if you are suggesting that maybe licensure isn't the way to go here. I'm certainly not suggesting that myself.

But do you mean that the FDA could possibly say if you follow FACT, NetCord, or AABB standards that that would be licensure? Or not put the license tag on the product at all so that we could

investigate other indications or other uses? Maybe not other uses, you know, other than the homologous use of the cells.

But exactly where were you going with your question besides reinventing the wheel of the standards that already exist?

MEMBER WOO: I'm not the FDA. I'm just on the Advisory Panel. I'm trying to educate myself.

It really has to do with all of this standardization of the product that is what I'm addressing to. Whether, you know, there is licensure, that is a separate issue.

Indication certainly should be we should consider broadening the indication to include non-hematologic diseases and so on. But that is a separate issue.

I'm just talking about product qualification.

CHAIR MULÉ: Mary?

MEMBER HOROWITZ: I think having the option of having FACT-NetCord accreditation or AABB or whatever set of standards that we would agree on are

appropriate would, because the FACT-NetCord standards are international and there is an increasing number of international banks who are getting accredited, would it help to address this international exchange issue because some of the provisions in the guidelines are so U.S.-specific, they are going to be a problem.

CHAIR MULÉ: Comment in the back?

MR. GIGLIO: Yes, I just wanted to ask the Committee or hope the Committee continues to keep in mind as they make their deliberations the following clinical scenario which I sort of alluded to in my initial presentation.

If you have a patient and there are two potential units out there, one from an accredited center or a licensed center and one from a center that doesn't meet whatever the licensing requirements are and from the center, the unit from the accredited center has an inferior cell dose and an inferior HLA match that is associated with a 30 percent survival in retrospective data versus a superior cell dose and a superior HLA match that might be associated with a 60 percent survival from our outcomes data, I would hope

that the clinicians, the transplant physicians and their patients wouldn't be forced to accept the unit that is associated with a 30 percent survival in our outcomes data from our retrospective data compared to one that is 60 percent survival, based on the licensing issue.

MEMBER WOO: Could I ask how often does that occur?

MR. GIGLIO: Well, I think that we look -- it's not necessarily so easy to find an appropriate cord unit. It can occur quite frequently. I can't give you a percentage but it can occur quite frequently. There are clearly superior --

MEMBER WOO: What does that mean? Once a year? A hundred times a year?

MR. GIGLIO: Oh, no, no, no.

MEMBER WOO: What does it mean?

MR. GIGLIO: Well, we don't know what is in a licensed or a non-licensed center. Right now we get cord blood units from a variety of different centers. So I don't know what centers would be licensed or not licensed. That remains to be see.

CHAIR MULÉ: Dr. Witten, do you care to comment?

DR. WITTEN: I just wonder if I maybe should just provide some clarification about what we think we're doing here just to help with the discussion. And if this is redundant to what you have already heard or understood, then I apologize.

But the plan is that cord blood banks will need to have licensure. And right now none of them are licensed. And so because there is going to be, you know, there is a requirement that is right now in abeyance for licensure for cord blood, FDA looked to see what guidance we could provide to industry to give them some idea of what kind of data and what kind of manufacturing they would need to follow to be licensed.

And in doing that, we did look at existing standards to try to take from what was best known, you know, in the community about best practices and how to make these products and what they are for.

The reason that we are having this meeting here today and also the reason why right now this

guidance is a draft guidance and it is open for comment is because we'd like to know not, you know, just generally what alternate scheme we might propose but for this guidance, you know, for example, I heard the comment that this would make it difficult for some banks to achieve licensure.

I'd like to know specifically what are some of the things that, you know, you might suggest that you think the guidance is too, you know, specific in some areas that might be difficult where there might be an alternate that is justifiable.

And also, I think there is no question that international units and also the historical units, if I can call them that, you know already banked -- I don't know what the term would be -- but historical units, that those are of enormous importance.

So that to the extent that there are some things that, you know, we should take a look at prospectively to think about how, you know, the international community is going, we would like to hear about that, too.

Now what we can't do, I mean I know this because it is something that we have discussed internally, there is no mechanism right now for a deemed approved status for accreditation by some group. I mean it is not that we don't encourage accreditation actually. You know we think these standards are a good thing. We think accreditation is a good thing.

But in a way, it's almost -- if you consider it the difference between encouragement and enforcement, you know, we have inspections and we have requirements. So I think what we would like to hear is, you know, specifically, your comments.

I mean you, as a, you know, committee on what in here, you know, you think that based on current practices or current best practices, international, you know, community practices, that you think that we should take a look at and consider modifying, that's why we're having this meeting because we'd like to hear about that.

And also I'd like to encourage, you know, anyone here or anyone, you know, in the room with what

I've just said in mind, to also take a look back at this guidance and see what would be useful to put in both from the point of view of cord blood banking and also I've heard a number of comments from, you know, the point of view of the practitioner community, you know what do you think, you know what do you think would optimize, you know, this guidance.

So I don't know if that helps clarify what we think we're doing -- okay.

DR. LAZARUS: And also along those lines, I just wanted to elaborate on one small point regarding the GMPs, where like Dr. Witten said, we are interested in hearing what we have in the guidance would, you know, need tweaking.

And with regard to the GMPs and the issue of retrospective demonstration of conformance with GMPs, in my presentation I outlined the GMPs. And in the guidance there is a lot more detail about ways that we recommend a cord blood manufacturer could comply with those.

So any one of those GMPs seems particularly problematic, we would like to hear that.

DR. WITTEN: Sorry, I just want to add one more thing because it has come up. And I think that maybe question one, although it was clear to us when we wrote it, it might not be entirely clear. And it came up during the open public session, I think. Someone made the comment about what's the alternative, you know, an IND?

And that may be, you know, what ends up happening with some of these. In other words, I don't think we want to create the situation where, you know, these can't be used. But what it will be, you know, if we have, you know, the implementation date for licensure, I would, you know, anticipate that that would be the other alternative.

CHAIR MULÉ: Mary?

MEMBER HOROWITZ: Just a question. I'm not a blood banker -- cord blood or otherwise. But I would be interested in hearing from some of them about the implications of requiring GMP, whether it is retrospective or prospective on the ability of banks to stay in existence and on the cost of banking.

CHAIR MULÉ: Donna?

MEMBER REGAN: Well, I'll just make a comment. I know that this is particularly challenging to cord blood banks, as I've heard -- not just cord banks but cell therapy labs in general -- with how to comply with GMP. Exactly what the definition is as it applies to the scope of the processing that occurs within that laboratory.

We know what the biologics are as far as particle counts and sterility testing in particular. As you are aware, you know, there are lots of folks doing the automated methods. But I know that is a challenge. And it's, I guess, more about the interpretation of how to comply with that. And then how it will be assessed when looked at.

I mean, does it have to be -- let's be real particular. GMP for -- do you have to classify an entire facility? A room? An area? A hood? You know exactly where does GMP -- where is it limited or what does it cover? So, I mean just in the physical facility and how to maintain and monitor that.

And then I've seen a lot of challenges with -- you do a lot of monitoring, and what does it

really tell you? And how do you then go back to a single product that you have used or how do you go back to a single product and reassess all of those qualifications when it is already frozen and, you know, ready to use.

So I don't say I have any answers here. I'm just saying I've heard those are the challenges that are out there.

CHAIR MULÉ: John, you have a comment?

DR. McMANNIS: Yes, my comment is, so we've got both a GMP facility and we also have a CORE facility, which is non-GMP. We have been doing --

CHAIR MULÉ: Who do you mean by we?

DR. McMANNIS: We being M. D. Anderson and a cord blood bank, so we've got both. But we have been doing an environmental monitoring study for over two years. We cannot see -- and we've got full environmental monitoring in the GMP. But in the core, we're doing it sporadically.

We cannot see a difference in sterility, nor can we see any correlation between what we see in the routine lab versus what is in the products.

Again, many of these procedures are done in biological safety cabinets.

And so I would say that, you know, in answer to Mary's original question, what is this going to cost, it is going to cost quite a bit more, you know, per product. Maybe two, three hundred dollars more just for the additional gowning, just for the additional testing, et cetera, that you need to do.

And I guess looking at the data that we have seen earlier this morning for the last 14 years, I'm not -- which I think every one of us would say none of this has been done to date under GMP facility conditions, I don't think it will add to the safety of those products. That's my opinion.

CHAIR MULÉ: Comments?

MR. QUAILA: Just one comment. I'm aware of a case recently in which two cords were transplanted that did not engraft. And neither of those units exhibited any colony-forming activity post-transplant. So the question is why.

In many respects, that's a very important two units to track backwards. Why didn't that occur?

And the question is, was it the patient or was it the units? There's certainly some evidence in this case that those units probably couldn't have saved any patient. Maybe not.

CHAIR MULÉ: Can you identify yourself please?

MR. QUAILA: I'm sorry. My name is Phillip Quaila. I'm the CEO of ThermoGenesis Corporation.

And so part of what this all about is to allow you to take circumstances like that and work yourself backwards to try and understand what happened. Transplanters choose these units on the basis of pre-freeze cell dose, largely, and HLA.

Well, the HLA doesn't change, but there may be a hell of a difference between the pre-freeze cell dose and what shows up when you thaw it out. And every transplanter in the room here is aware that there can be dramatic differences between what you thought you were getting and what you actually got.

And I know there could be granulocyte, you know, differences. I mean big quantities of

granulocytes that don't tolerate freezing but when you have no colony-forming activity, how do you track that back and try and find out why?

And there is a whole series of questions you need to ask to look at all the suspect areas where bad things can happen to these units starting right from when you collect them. There are a whole variety of different steps that can take place.

And unless you have that information, you have no ability to do continuous improvement on the manufacturing. You've got to track it back and find the correlations between processing activity and the fact that you have no colony-forming activity here.

And this regulation, I think, that the FDA anticipates, I think, will be of great help in that respect.

CHAIR MULÉ: Dr. McCullough and then back to Mary.

MEMBER McCULLOUGH: I was going to try to elaborate a little bit on the answer to Mary's question. I also would agree with Phil that this kind of regulatory approach will be helpful.

In some ways, I think there ought to be a GMP-lite for cord blood. For instance, with facilities, I mean I've not had the pleasure of being able to visit Pablo's facility, for instance, but it seems to me that a traditional blood component lab like we find in most large blood banks is an acceptable kind of facility in which to do this.

You don't need class 10,000 air and all that sort of thing. And it really applies to the minimally manipulated kind of products as opposed to the highly complex manipulated products where you do need class 10,000 air and all the rest of that sort of thing.

On the other hand, the kind of personnel and training and documentation and those aspects of GMP really are pertinent, and it allows investigation of problems. And it allows the pursuit of the sort of questions that Phil has just mentioned.

So in a way, if the Agency is open-minded enough to look at exactly how a cord blood bank would propose to meet GMPs and take that into consideration with what they are actually doing, then I think this

is a helpful step to improve safety for the patients in quality. But even at that rate, it's going to increase the costs.

MEMBER HOROWITZ: I guess I'm asking for a pragmatic approach that doesn't just, you know, put what we traditionally consider as GMP, greatly increasing the cost, greatly decreasing the ability of some banks to participate in the process and, therefore, decreasing the availability of units, you know, for not a lot of benefit.

So everything is always risk benefit. But I totally agree with what you are saying in terms of having a pragmatic approach to what is required.

Like I said, I'm not a banker, so I can't go line by line and say this yes, this no. But my perception from talking to a lot of people in the field is that these requirements are going to be onerous for a lot of people and impossible for some banks.

In terms of two units that didn't have CFU, that screams to me transplant center, transplant center, transplant center, because what is the

likelihood of having two units with no CFU, you know, collected at different times, stored at different times.

And one of the things we have to realize is that the banks only take care of those units up to a certain point. And some of these things that we are looking at, post-thaw counts are, well, you know, it's not the banks that are doing the thawing.

And also the SCDOT will be tracking all adverse events such as these. And helping to investigate them.

CHAIR MULÉ: Comment in the back. Please identify yourself.

MS. LOPER: Thank you. I'm Kathy Loper, AABB. And during the AABB public comment to the guidance, those comments focused specifically on the guidance and not on any political standardization-type issues that the field might be undergoing now.

So I'd like to respond to Mary's question actually from my perspective of -- I don't know, 17 -- I don't want to admit this -- 18 years in the blood banking and cell therapy processing field.

Standards are, in fact, voluntary. And they have evolved over time based on what we think are best practices. Since 1996, unless I'm mistaken, FACT is on their second edition of standards. Just came out with the third.

AABB standards are now revised every 18 months but they were every two years. And so that means that what we think the best practices are today are not the same as what they were ten years ago.

So something as simple as facility or equipment cleaning that we would all agree is just a very basic tenet of a quality system, today under GMP and GTPs, in addition to cleaning, there is a log sheet by the biological safety cabinet, by the centrifuge, where every product is logged in, who cleaned it. It is documented in between products.

Five or ten year ago, the best facilities may have just had a procedure that said the equipment and the facilities are cleaned daily or weekly or monthly. And they just followed the procedure. There wasn't documentation with every product and with every piece of equipment.

And so I think that the problem with requiring retrospective documentation that these products were processed under GMPs is people didn't do it. They did the best practice that they had at the time.

And so I think that from a practical standpoint, to answer Mary's question, it's just not possible unless you can say, well, we did have procedures that address all of the elements in the GMP. So we did have something for cleaning. We did have something for equipment.

We did have something for personnel, although we may not have gone and looked at training records for the collection staff of an outside facility like we might do today.

DR. LAZARUS: I'm just going to jump in with a very quick comment about GMPs proving to be a very interesting subject of discussion. Just to make the point that, for example, the GMPs don't specify a particular class for a laboratory or particle count. But rather rely on the concept of environmental control commensurate with the relative openness versus

closedness of the processing system.

So within the GMPs, there is some degree of flexibility. And where in our guidance we tried to suggest some methods and factors that would be addressed in the biologic license application, you know, we are very interested in hearing that feedback.

And where we can clarify some of these issues to enhance this ability to establish some comparability in retrospective assessment of documentation of compliance with the requirements, we intend to do that.

CHAIR MULÉ: Okay. Savio?

MEMBER WOO: Well, I was just going to comment that retrospective, that's tough to do. I mean you know we have all these cords, they are stored somewhere. Are we going to just junk them? I don't think so.

But to me it is more important thing about prospective. What kind of GMP or GMP-lite are we talking about that would be not so onerous to the banks and yet still ensure the quality of the products? I'm more concerned about the prospective

side of it because that is going to be years and decades.

CHAIR MULÉ: Okay, let me ask FDA. With respect to question one, since we're moving on time here, do you have what you need from this discussion so far? Do we need to spend additional -- you're okay? Okay.

So if we could put up question two. So question two has to do with clinical indication in the draft guidance with respect to describe any additional data of which you are aware that could potentially support additional indications -- I assume beyond hematopoietic reconstitution -- in patients with hematologic malignancies.

Go ahead, Joanne.

MEMBER KURTZBERG: Well, I, again, want to make a plea to include the nonmalignant indications that are traditionally already indications for bone marrow transplantation as indications for cord blood. I think it will do a lot of damage to restrict this licensure just to hematologic malignancies.

When you think about transplantation

medicine, getting insurance approval, bringing patients to transplant quickly, not having to appeal to insurance companies because cord blood is licensed for one but not another of the standard indications for hematopoietic transplantation.

And in that vein, transplantation for a hemoglobinopathy, for marrow failure, for immune deficiency, and for metabolic diseases are all standard indications for marrow transplantation and are also already shown with reports in the literature in very good journals to have very positive outcomes with cord blood transplantation.

And these are generally rare disorders. There are not hundreds of thousands of cases. In some instances, there may be ten a year -- or 20 or 40 -- but they are very important. Cord blood is lifesaving in those indications. And there's no reason theoretically or practically or in the data that is available to say there would be anything but a benefit to patients if these indications were approved.

There are papers that can be provided to you. I can give you a metabolic presentation right

now if you want it. And I just think that it is an oversight not to include those diagnoses.

MEMBER HOROWITZ: Yes, I agree with you. There is really no rationale to restrict it to hematologic malignancies and not the other standard nonmalignant indications for hematopoietic stem cell transplantation.

I think we saw data this morning suggesting that there is really not a marked difference in outcome whether we're looking at nonmalignant diseases or malignant diseases. I can say that currently in children under the age of 16 in some data I asked to be sent to me this morning, that the number of cord blood transplants being done for nonmalignant diseases actually exceeds the number of adult donor transplants being done for nonmalignant diseases in the unrelated donor setting.

So, you know, you'd be taking -- there is really no reason to distinguish. If we're talking about hematopoietic reconstitution in the transplant setting, homologous use, whatever is an indication for a bone marrow transplant should be an indication for

a cord blood transplant.

MEMBER KURTZBERG: I'd love to just give one example. New York State started a pilot program screening newborns for Krabbé disease because it has been shown that if you can transplant a newborn with Krabbé, they live, they walk, they have normal intelligence.

And if you don't transplant a newborn and you wait until they have symptoms, although you prolong their life, they are vegetative. They are fed by a G-tube, they never walk, they never talk, they can't see, and they have a really poor quality of life.

And if you don't transplant them at all, they die by one to two years of age.

So New York State implemented a newborn screening program. They started in August. They screen 12,500 babies a week. Last week they identified the first true positive baby.

The baby was brought back to the pediatrician to be retested at ten days of age, was referred to our center at 14 days of age, arrived at

16 days of age. And because the NMDP had already agreed to a program where when the retesting for Krabbé was done they would do HLA typing, the baby's donor was identified and tested by the time the baby was 18 days of age. And the baby started chemo at 20 days of age and will be transplanted by 30 days of age.

And there is no way you could do that with an adult donor. It is just not physically possible to get things through the system that quickly.

Now this baby got a dose of 500 million cells per kilo because the baby weighs 2.5 kilos. And, you know, cord bloods for that size person are very big. And he actually got a nine of ten match. He's Hispanic.

And, you know, all the many other barriers were in the way. New York State Medicaid approved his transplant. So I mean barriers can be overcome. Things can come. This is the right therapy for this baby. But it couldn't happen with an adult donor.

And we can't have programs in our country that are already going forward with things like this

and then have the FDA not license cord blood for that indication.

CHAIR MULÉ: Kurt?

DR. GUNTER: Well, I think we all agree that the indication should be expanded. We know the FDA is a data-driven agency, and my understanding is in the initial data submitted to the docket, there just weren't enough safety data on nonmalignant diseases.

So maybe we should ask the FDA, you know, what kind of data submission it would take, how much data. And once we get an answer to that, we can talk about how that information should be given to the FDA, is my suggestion.

DR. WITTEN: I'll just say that we certainly think this would be an appropriate comment to the docket on this draft guidance document, and the better documented the comment the better. In other words, a review -- a suggestion, literature, something.

In other words, if there is something specific somebody want to offer up as, you know, their

proposal, what to add, and they have some literature that they want to provide to support that, that would certainly be appropriate. And you could submit it to this draft guidance docket.

CHAIR MULÉ: Joanne?

MEMBER KURTZBERG: Could I just go on record -- and we will submit this -- but there are two papers in the New England Journal of Medicine. There is a paper on biology of blood and marrow transplantation. There is a paper reporting the Cobalt experience -- all metabolic. These can all be provided to you.

I think you already have in the docket the Cobalt data in addition to the initial New York Blood Center data. And we'd happy to provide you dup data on 160 patients.

DR. WITTEN: I think a comment to this, you know, guidance with a summary of what you think the available literature information is would be useful.

MEMBER HOROWITZ: We will except that the absolute numbers are going to be small because these

diseases are uncommon. And the numbers of transplants that have been done for them, whether from cord blood or otherwise, is relatively small especially when they are considered as individual diseases.

CHAIR MULÉ: Okay. We'll move on to Mary. Did you have a comment?

MEMBER LAUGHLIN: An additional comment is that in the aspect of providing licensure of what is an evolving science, how best to do that and not inhibit the evolving science and not inhibit patients from access to a potentially lifesaving treatment, I agree with the recommendations to the Agency that the recommendations per FDA would provide that this new graft source -- indications for this new graft source would parallel indications with "conventional" grafts from adult donors.

That would avoid some of the aspects of specifically naming 120 diseases that may be rare. And it would be an appropriate guideline. The indication is allogeneic transplant. And then the graft source is identified.

CHAIR MULÉ: Okay. Let's move on to

question three which has to do with recommendations with respect to assisting cord blood manufacturers in preparing information to be submitted in the BLA for cord blood. Recommendations?

Donna, do you have a comment?

MEMBER REGAN: I guess a comment would be that the guidance is very well written. And most of the very technical pieces would be addressed in the comments that you will get back. And I'm confident each one of those will be given the attention that they deserve.

So at this point, I think just maybe modifying the document here and there, depending on the comments you receive, would be appropriate.

CHAIR MULÉ: Other comments?

Dr. McCullough?

MEMBER McCULLOUGH: I don't remember if there are any words like this in the guidance or not, but you might want to urge banks to communicate with you as they are starting the process to put their application together because anyone who wasn't here to listen to the discussion might not be very savvy to

how to present information to you about their facility or the way they are doing GMP. And I think you could provide a lot of help and a lot of guidance in the very beginning if you would urge banks to start communicating with you right away, you know, as they are first thinking about this, especially with the older units as we discussed.

CHAIR MULÉ: Stan?

MEMBER GERSON: I did hear the word onerous used a few times, and my hunch is it went through people's minds much more than it had been heard.

And given the fact that FACT has at least already accredited four U.S. banks, it might make sense to encourage some alignment of the response to a licensure request that tried to not reduplicate in a completely different format the approach taken to responding to the guidelines.

So if there is some ability to get the groups together to align those efforts, it would seem to be to be a positive for everyone.

CHAIR MULÉ: Donna?

MEMBER REGAN: I have a question and clarification about the timeline for all of this. I know you can't, you know, definitively say right now at what point, you know, licensure would be necessary. But it also feels like we might have to continue our INDs for a while.

How will the FDA deal with enforcing licensure? I guess that is a question in a lot of people's minds. If at some point, if you want to continue to distribute units for these applications must you be licensed? And then the rest of your inventory can go out under an IND.

You know I guess some of that time frame and some of those questions aren't clear at this point but probably will be later.

DR. WITTEN: Well, I can't tell you what the time frame will be but you have the right general idea. That at some point, you know, when the guidance goes out in final, we'll also announce a date for implementation of the requirements for licensure. And at that date, people would have to either be licensed or under IND.

So what you outlined is -- yes, that is what we anticipate.

MEMBER REGAN: So there's room for both scenarios at this point?

DR. WITTEN: That would be my general concept.

MEMBER McCULLOUGH: And just for the rest of the Committee's information -- and correct me if I'm wrong, Ellen, but I think a fair amount of cord blood banking these days is not under IND. IND is not required now, right? And so a moderate amount of cord blood units are being provided not under IND? Or am I wrong on that?

DR. LAZARUS: I can't answer the second part of your question with regard to numbers but I can confirm your statement that at the current time, we are in a period of delayed implementation of IND requirements. So cord banks are not required to operate under an FDA-accepted IND.

However, as you all know, it has been publicly explained by a number of cord banks there are several who do currently operate under FDA-accepted

INDs.

MEMBER McCULLOUGH: But just so the Committee is aware then once licensure goes into place, anyone who is not licensed will have to start operating under an IND. And that probably will impact a number of existing cord banks.

MEMBER KURTZBERG: I'm not sure it really will, to be honest with you. I think most banks are either under their own IND, the NMDP IND, or well, those two things. Or some banks are under several INDs. I can't think of one that isn't covered in one of those two umbrellas right now.

CHAIR MULÉ: Savio?

MEMBER WOO: But I thought eventually we will have to get the licensure and the IND. It is a matter of time. It is not a question of whether. That's why we are all here. So yes, there will be -- there may be some banks that will not qualify and so on.

But as long as there is sufficient time for those banks to rise up to the standards, they should be encouraged to do so rather than keep saying

oh, well, you can continue to operate the way you are. Don't worry about this regulation.

CHAIR MULÉ: Okay. The last question has to do with HPC-A. So similar types of issues related to demonstration of safety and efficacy. And consideration of approaches to BLA. Comments about that? Similar to cord blood?

MEMBER HOROWITZ: It's not very similar to cord blood, I'm afraid. I mean there is a lot less manufacturing that is going on here. You are leukapheresing a donor and then you are putting those cells in a patient, if we are talking about the minimally manipulated setting.

So, you know, a lot of the things that are in that guidance document are not really applicable, and I don't see how you -- I mean -- and then what is the difference between doing that in a related donor and doing that in an unrelated donor? I have a hard time.

You know, cord blood, you know, you have to collect them, process them, store them for a really long time, and then make sure you get the right one

out and transport it frozen, you know, to -- in good shape.

And it is a whole lot different, you know, with an adult donor where you identify the donor and the donor comes into an apheresis center. And, you know, if it is in an apheresis center that is accredited, I don't see where all these guidelines apply.

MEMBER KURTZBERG: I agree with Mary. I think, you know, I'm aware at our center we probably process 20 or 30 cord bloods a day coming in from eight different hospitals with collectors all over the place.

But we may get one or two apheresis donors. They're sitting right in our, you know, room right next door. Their product gets carried to the patient. We take a little bit off to do some testing, but it is never frozen. You know it is a totally different -- one-to-one directed donor kind of setting.

MEMBER HOROWITZ: I mean let's just take one simple thing. You would never -- you would not,

not use that product if it were contaminated, you know, if it had a positive culture. First of all, you probably wouldn't know about the positive culture until afterwards in the patient.

So your product, your sterility cultures come back and there is a bacteria growing. Well, you have a patient that has no marrow left, right, and you are going to put those cells in that patient, no matter what.

And let me just tell you that we did an analysis of several thousand bone marrow and peripheral blood transplants. And we looked at those which had positive cultures versus those that did not. And the ones with positive cultures did a little better, actually.

It was a small difference. Because there were thousands of patients, it was statistically significant. So, I mean so there are a lot of things that are different. And I don't know that we can, in a hearing like this, address all those things that are different about adult donor peripheral blood transplants versus cord blood. But it's just a whole

-- the issues are different.

CHAIR MULÉ: Dr. Miller, do you have a comment?

DR. MILLER: Yes, John Miller from NMDP.

I agree with those comments, and in the data we've submitted to the docket for our PBSCs, if we look at 100-day survival and you look at product-related factors, donor-related factors, and recipient-related factors, there are no product-related factors that in the multi-varied analysis are significant on patient survival.

And so really what you are thinking is there are donor-related variables, for example, gender, their own CD34 count that impacts the product you collect. And as Mary says, the product you collect is the one you are going to use. And then you have all the clinical variable as well.

So when you are thinking about what kind of standards you would apply to a product, it is really tough to come up with what they would be.

CHAIR MULÉ: Stan?

MEMBER GERSON: Could I just add, I think

this conversation is actually quite logical. What was missing was the logistic. And that is that the number of sites performing this procedure is quite large.

It may be unregulated but it is quite large, doing a quite good service with a low, remarkably low rate, as we've heard, of with intra-institutional or cross-institutional related product failure.

I don't know how one would implement a licensure procedure without a major negative impact.

CHAIR MULÉ: Dr. McCullough?

MEMBER McCULLOUGH: Three points. One is to reinforce what Mary said. If you think about product release criteria, you have to think about it totally differently than cord blood because you won't have time to get the results back on a lot of the things that would be considered release criteria to put a unit of cord blood into the usable inventory. So the thinking has to be a little different of what you can actually get back logistically in relation to that apheresis.

One other thing though that is quite different. And I don't know how the agency would approach this, quite different with apheresis donors is they are being given a medication, several medications, as you know from a week or two ago, I mean most of these donors are getting GCSF for mobilization of their cells.

And so it is a little different setting in that we're subjecting those donors to some minor or maybe even ultimately theoretical substantial risks. And so somehow that puts a little different spin on all this.

And then the other thing to say, and maybe if it is appropriate, if John Miller has any comments about this, stem cell donation by apheresis isn't innocuous. I mean there are some serious adverse events that do occur, although rarely. And I think the NMDP has that kind of data.

So it would be another thing that the Agency would want to include in their thinking about whether that data shows anything that would suggest that some kind of requirements would minimize the

likelihood of those sorts of bad things happening.

CHAIR MULÉ: Dr. Miller, do you want to comment on that?

DR. MILLER: Yes, we do have a lot of data on kind of the patient adverse events that happen. I think the challenge is predicting which donor is going to have that set of adverse events ahead of time. And so we do see some of the common citrate toxicities, the GSF-related bone pain is very, very common. In fact, the majority of donors have that.

I think the challenge, Jeff, is to try to figure out which donors are going to have that. But I think maybe the other point that you are trying to make is we have an ethical issue that we really have asked for a very big commitment from our PBSC donors where many of them do have serious bone pain, nausea, vomiting, and the potential long-term risks that are theoretic of hematologic malignancies. So there is that donor aspect to it.

MEMBER HOROWITZ: But you could say the same thing about bone marrow. And, in fact, the

incidence of long-term problems, although they are not the theoretical leukemia that gets a lot of press, you know, in terms of musculoskeletal problems is actually higher in bone marrow donors as opposed at PBSC donors.

So, you know, we're going to regulate one but not regulate the other. I mean in the U.S., all of these donors are coming through the NMDP, the PBSC donors, which has to accredit the collection centers -- qualify the collection centers, look at the collection center outcomes, and is following those donors long term. What more do we want to do?

CHAIR MULÉ: Other comments?

E.J., would you want to share some of your thoughts about the briefing document? Do you have any thoughts about that? E. J. Shpall?

DR. SHPALL: Well, I first of all think it has been extremely well-written and carefully thought out. And I applaud the FDA for taking the time and effort to really talk to the groups who are invested in this. And I can say, coming FACT-NetCord, we did -- we have had a lot of dialogue with

Ellen both for this and outside of this. And so I think they have been very thoughtful.

No question there is a need to protect our patients, but I am concerned, as I said in my initial comments, about preventing good units that could come into this country and until we have more details on how we would work around that, I think we can't really comment completely on how this will go because I still don't have a good sense from Ellen and the FDA today on how we would get a unit into our patients that wasn't meeting the specifications.

I think what is fair to say is if you are meeting FACT-NetCord standards and you've invested a lot of time and effort in trying to make yourself into a good bank, you probably can comply with a lot of the standards or the regulations as they are proposed.

The standards never specify a cell dose or a CD34 dose. That's different. And I think that is, again, something to be debated.

I agree completely with Joanne, that we need to broaden the indication because more and more

patients with non-hematological malignancies will be getting cord bloods, and that is a need that has to be proffered.

And beyond that, I think we need to talk about GMP. As John said, it's really expensive, and so if putting yourself in a GMP environment is not going to really help the contamination of the products, I think we need to have FDA be flexible and talk about that as we move forward.

So I think those are my major comments at this time, unless you had specific questions, James.

CHAIR MULÉ: No, just comments, thank you.

Dr. McCullough?

MEMBER McCULLOUGH: One other question about the apheresis -- beginning thinking about licensure. And I think it was Dr. Miller who mentioned that possibly some or a lot of the presently-certified collection sites would not want to go through the process of getting licensed. And this could greatly reduce the number of locations where blood cells -- stem cells could be collected.

Thus maybe making some donors even unavailable.

It seems to be an important issue. I don't really have any solution to it but, you know, I'm sure that you all at the FDA will be talking to NMDP and others to sort out how, as you develop guidance, you can make it realistic so that you don't end up essentially shutting down a lot of the locations where blood stem cells are collected.

You have to have some sort of balance that you want it done correctly and well in a structured mechanism but also it works against the patients if we end up losing donors because of the location they would have to go to donate.

CHAIR MULÉ: Okay. Are there other comments? For the FDA, do you have what you need? Do you have any other specific questions that the Committee could comment on? Okay.

Savio?

MEMBER WOO: Just for my education again, how is blood transfusion regulated? I mean we're talking about taking cells from one patient and putting them in another. Theoretically, it is also

under GMP regulation.

So I was just wondering why is HPC-A not regulated kind of just like the blood transfusion? I'm just asking because I don't know.

DR. WITTEN: I can give a little answer to that. And I think Ruth maybe or Ellen could give a more -- Dr. Solomon or Dr. Lazarus could give a more detailed answer perhaps.

But basically, the HPC-A come under human tissue regulations. And bloods are also regulated. They are regulated under the bloods regulations. So, you know, there are some similarities from the regulatory schemes but there are some difference, too. And they just fall under different categories.

But how specifically bloods are regulated, I can't answer that.

MEMBER WOO: I'm just asking can we consider similar kind of process of regulating HPC-A and blood transfusions is what I'm asking.

DR. SOLOMON: Be careful what you ask for. Okay, blood establishments that engage in what we call interstate commerce all have to get licensed.

And each product gets a license. Then we have the intrastate blood banks are registered but don't have to be licensed.

Obviously, the apheresis products may or may not travel interstate. But it turns out that if we are considering them HCT/Ps, the interstate-intrastate distinction is not there for HCT/P.

DR. WITTEN: Anyways there is another inspectional system that applies for the blood banks in the individual states, right?

DR. SOLOMON: Yes.

MEMBER McCULLOUGH: Can I add to that? I think there are many similarities if you look at it from the broad sense. The requirements to evaluate the donor, to test the donor for transmissible diseases, personnel requirements, documentation, process control systems, conceptually that is exactly the same thing that they are doing here.

CHAIR MULÉ: Other comments? Yes?

DR. WARKENTIN: So the one thing about --

CHAIR MULÉ: Can you please identify yourself?

DR. WARKENTIN: Oh, sorry, Phyllis Warkentin. This time I'm from the University of Nebraska Medical Center. And I think the one thing that is appealing about the blood system is that the manufacturer doesn't have to be concerned about the indications. So the Red Cross makes my red cells and I'm the Blood Transfusion Director and I buy them. And people in my hospital transfuse them.

And the manufacturer never has really too good of a clue what the surgeon is doing with them. And I think that is the one thing in the blood system I think that kind of -- it is what we've talked about a lot today, about broadening the indication.

So I guess that was my only comment because I know a lot of the blood regulations are complicated. And they are held to a pretty high standard as well. But that was the one difference that might help us.

CHAIR MULÉ: Kurt?

DR. GUNTER: Just one quick and hopefully helpful suggestion. Normally in other blood development programs, the FDA is very helpful and

available for pre-BLA meetings. So I'm sure you are planning to have pre-BLA meetings with banks that are considering this route.

And I just want to encourage the FDA to get the word out to cord blood banks who may not be aware that you are available to meet with them and provide advice. Because there are a lot of unknowns about the establishment and, you know, having a meeting before a lot of money is invested in building or rebuilding an establishment can be very helpful.

CHAIR MULÉ: Thank you.

Doris?

MEMBER TAYLOR: I'd just like to ask a question and I'm really not trying to open a new conversation. But if this guidance document is accepted for minimally manipulated samples, will the same sort of guidance document be created if indications are expanded beyond hematologic disorders?

Meaning if some of these minimally manipulated samples are begun to be used for regenerative medicine, will licensure be required?

Has that conversation begun?

DR. WITTEN: I'm not completely sure what your question is, but I think I can answer it anyway.

Okay, so let me --

MEMBER TAYLOR: CD34+ cells for cardiac repair.

DR. WITTEN: Oh, that's a different question. Yes. Okay. So your question is, how does this guidance relate to products being used for nonhomologous use?

MEMBER TAYLOR: Right.

DR. WITTEN: And you are talking about the cord blood?

MEMBER TAYLOR: No.

DR. WITTEN: This? Okay. Well right now this is just --

MEMBER TAYLOR: PBMCs.

DR. WITTEN: Okay, this doesn't exist right now. So we're just at a thinking stage of what we could put in it, would want to put in it, and what it would be. So I don't think that could -- you know, that couldn't be answered. It depends on what

the scope of it was and, you know, what information there was to support it.

CHAIR MULÉ: Okay. Other comments? All right. So I think we're done.

On behalf of the FDA, I'd like to thank all the Committee members, again, for your time and sharing your knowledge with us as well as the invited speakers today. And also those in the audience who participated.

And I know that Savio learned a lot today.

(Laughter.)

DR. WITTEN: And I'd like to thank that panel and the Committee and the public on behalf of the FDA, too.

(Whereupon, the above-entitled meeting was concluded at 2:28 p.m.)