U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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WORKSHOP ON IMPLEMENTATION OF UNIVERSAL LEUKOREDUCTION

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FRIDAY, DECEMBER 10, 1999

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The Workshop was held in the Natcher Auditorium, NIH, Bethesda, Maryland 20892 at 8:30 a.m., Jong-Hoon Lee, M.D., Chair, presiding.

PRESENT:

JONG-HOON LEE, M.D.	Chair
CAPTAIN MARY GUSTAFSON	Speaker
EDWARD SNYDER, M.D.	Speaker
CAROLYN JONES	Speaker
BETSY POINDEXTER	Speaker
LARRY FENNER	Speaker
STEPHANIE NORRELL	Speaker
WILLIAM ANDREW HEATON, M.D.	Speaker
CELSO BIANCO, M.D.	Speaker
JIM MacPHERSON	Speaker
JAY MENITOVE, M.D.	Speaker
DENNIS GOLDFINGER, M.D.	Speaker
JOHN WHITBREAD, PhD	Speaker
HARVEY KLEIN, M.D.	Speaker

ALSO PRESENT:

JUDY CIARALDI
LES HOLNESS, M.D.
JAY EPSTEIN, M.D.

I-N-D-E-X

P-R-O-C-E-E-D-I-N-G-S

(8:34 a.m.)

DR. EPSTEIN: I'd like to ask people to find seats, so that we can have a nearly on-time start. We have a full day ahead.

I'm Jay Epstein, Director of the Office of Blood Research and Review at CBER, and it's my pleasure to welcome you and also to thank you for making the effort to come and work on this important issue.

This is, as you know, a public scientific workshop on implementation of universal leukoreduction, and I'm sure most of you are aware that FDA brought the question whether we should recommend universal leukoreduction to the Blood Products Advisory Committee way back in September of 1998.

More specifically, we asked the Committee for its sense of whether the available scientific data supported the utility of universal leukoreduction, absent any question or consideration of potential benefit to reduced risk of Creutzfeldt Jakob Disease or a new variant of Creutzfeldt Jakob Disease.

The question was pointed in that way, because we were dealing with the fact that there had already been recommendation in the United Kingdom, I think dating from July '98, to phase in universal

leukoreduction over a two-year period as a theoretical precaution against new variant KJD, but this was very controversial; and we didn't think that we could have a scientific position on that point.

Subsequent to that, both Canada and New Zealand have taken public policies on universal implementation of leukoreduction for non-leukocyte cellular products of blood.

The outcome of our discussion at that time was a very strong endorsement of leukoreduction -- The vote was 13 in favor with three abstentions -- on the basis of numerous individual benefits, some better established than others, those best established including prevention of febrile non-leukocytic transfusion reaction, HLA, alloimmunization and reduction in CMV risk.

Numerous other benefits were discussed but, as I say, are less well established, including perhaps mitigation of immunomodulatory effects of transfusion, as well as other effects due to the process related to producing cytokines.

So I think we come here with already a scientific consensus point of view that there is overall a positive risk/benefit ratio or benefits/risk ratio for universal leukoreduction, but we are still

left with a broad spectrum of implementation concerns, many of which are logistic.

They deal with defining the proper conditions for carrying out leukoreduction. I think it was clear from the data presented in September '98 that there is better quality of the leukoreduced product if it is done as a controlled pre-storage operation in the blood bank.

Also, we reviewed the issues of toxicities that have been associated mainly with bedside filtration and recognize also that there is less variability to the residual leukocytes if this is done in the pre-storage controlled environment.

We are also aware that a decision to recommend universal leukofiltration or leukoreduction by other equivalent means translates into an unfunded mandate to the blood industry.

We know that there is already voluntary use of leukofiltered products for high risk recipients. This has been medically established and is used throughout the world. However, the recommendation or perhaps eventual regulatory requirement for leukoreduction would create a rather large economic burden.

From the FDA point of view this, of course,

would not be a reason for us to shy from a recommendation, if we felt that it was necessary for public health and optimal use of blood products. However, we are mindful of that concern, and indeed in the larger context of the Public Health Service, which has within it the HCFA Medicare funding program, there is a lively dialogue ongoing about mechanisms to provide appropriate reimbursement for advancements in blood safety.

So whereas that's not a key focus for today, we do understand that there may be opinions and needs expressed in that area, and FDA's response would be to convey these to the parts of the Department of Health and Human Services where response may be needed.

So I just also want to take a moment to specifically thank the real organizers of the conference, particularly Jong Lee who heads our Blood and Plasma Branch in the Division of Blood Applications, and again to thank you for your participation and the comments that you will provide to us throughout the day.

So let me then turn the podium over to Mary Gustafson, Director of our Division of Blood Applications, who has some prepared opening remarks. Mine, of course, were off the cuff.

CAPTAIN GUSTAFSON: Thank you, Dr. Epstein.

I, too, want to welcome all of you to this 459th CBER sponsored blood related workshop for calendar year 1999. Joe Wilczek just gave me a look that it does have a transcription, and perhaps I should clarify that that was really a joke. It just seems like we've had that many workshops.

Because of our heavy workshop schedule, we are most grateful that you have taken time out of this holiday season to come and be with us and to share your thoughts with us on the important issue of implementation of universal leukoreduction.

Dr. Epstein gave you the background information of our Blood Products Advisory Committee recommendation from September of 1998, and also the world scenario. So I won't repeat any of that.

I do want to stress that we want to have an interactive workshop today. We are -- This is not a workshop where we are going to give you a final draft document and you are just to listen to what we say. We are just in the preliminary stages of putting together some guidances, and we really do want your input at this preliminary stage.

I, too, would like to thank Dr. Jong Lee for organizing and the Blood and Plasma Branch staff

members who have also been on the organizing committee and have arranged the speakers for today.

I especially want to thank the speakers who have agreed to come and share their thoughts and also their experiences in implementing leukoreduction either before the BPAC recommendation or after the BPAC recommendation, and a special thanks to Joe Wilczek who is a member of our Policy and Publications staff, who has been Mr. Workshop for this year. Whether it's been a contracted effort or one that we have put on completely internally, Joe has made sure that everything runs smoothly from soup to nuts in the organization of the workshop.

In terms of housekeeping, the workshop is scheduled in four sessions today. We have two breaks, morning and afternoon, and a lunch break.

There are restrooms and telephone facilities on this floor. There's a cafeteria here in the Natcher Building. The weatherman is telling us that by Noon today we may have some rain. So you may want to take advantage of the cafeteria. If it's not messy outside, there are numerous wonderful restaurants in Bethesda. There's even a MacDonald's across the street at the Navy base.

The room is set up so that we have

microphones in each aisle, and once again I do want to stress that we want to hear your ideas, your thoughts, and your comments on what is presented today. We should have ample time in the last session to have a good discussion on what has been presented today.

So with this, I'll turn the meeting over to Dr. Jong Lee, who will present the goals of today's workshop and an overview of today's schedule. Thank you.

CHAIRMAN LEE: Thank you, Mary.

If you absorbed every information presented by Dr. Epstein and Mary Gustafson, I think you're pretty much set for a background and overview. He gave a brief -- as usual, a brief but very comprehensive overview of why we are here and where we are with respect to universal leukoreduction.

I'll try to go over in a little bit more detail the background of this topic, and also present a more detailed overview of today and present some workshop goals.

I have to thank the committee members who have assisted me and provided invaluable guidance in shaping and designing this workshop: Of course, Mary Gustafson, myself -- that long name is actually just pronounced "John" -- Les Holness who will moderate

Session II; Judy Ciaraldi who will moderate Session III; Joe Wilczek who you well know by now; as well as the remainder of the workshop committee, Linda Alms, Karan Blum, Marla Cohen, Gil Conley, Mary Ann Denham, and Janet Ishimoto, Carolyn Penny, Monica Yu and Ken Zemann who has assisted me in critiqueing the workshop design as well as recruiting the speakers.

First of all, the definition of universal leukocyte reduction: By universal leukocyte reduction, I think we all agree that we mean leukoreduction as a routine, integral step in blood manufacturing. In other words, this is to be a GmP step for generating whole blood, red blood cells, and platelet units for transfusion.

We also mean that leukocyte reduction is to be performed pre-storage and also, of course, we mean that this is to be applied only for blood for transfusion use.

How do we get to where we are today? I think there has been an ongoing dialogue for several years. Some of the more recent events: Starting with workshop in March of 1995, the regulations and licensing criteria were discussed, and at that point leukocyte reduction was discussed as a way to produce special products that bear a special labeling.

Subsequent to that, two years later, the issue was presented before BPAC where leukocyte reduction was discussed as a special indication in terms of its effectiveness against reducing the incidence of transfusion transmitted CMV.

Following that, in September of 1998, universal leukoreduction was first introduced as a public discussion, and discussed whether or not this should be considered as a new GMP issue, and we are gathered here today to discuss the implementation steps as to how best to adopt this, potentially adopt this as a national blood policy. The decision has been made to go forward, but it's not clear exactly how to proceed.

In developing public consensus, at BPAC the scientific basis for the risks and benefits of leukocyte reduction were discussed, and the charge to the BPAC was to discuss the scientific basis, irrespective of concerns for CJD or new variant CJD, and also, of course, outside the constraints of cost discussions.

Depending upon the outcome of the BPAC, the plan was to proceed -- to potentially proceed to examination of the issue in the context of new variant CJD at the TSC Advisory Committee, and then to follow that up with potential examination of the cost and

availability issues at the PHS Advisory Committee.

The question presented to the BPAC members, the specific wording, is the following: Is the benefit/risk ratio associated with leukocyte reduction sufficient to justify the universal leukocyte reduction of all non-leukocyte transfusion blood components, irrespective of the theoretical considerations for transfusion transmitted CJD?

As Dr. Epstein already mentioned, the BPAC vote was 13 to none in favor of universal leukocyte reduction with three abstentions. The consumer and industry nonvoting representatives agreed with the Yes vote.

In analyzing the way in which the BPAC members voted, however, you might look at some of the scientific discussions that were held, and as a summary it was clear that the only FDA approved indication for leukocyte reduction was the febrile non-hemolytic transfusion reaction and the scientific basis for that was adequate and, of course, that's why it led to the approval from the FDA for labeling. However, if you consider this in the context of relative clinical importance to the typical transfusion recipient, not to say that febrile transfusion reactions are not important, but in terms of relative importance it was

rather low.

Some of the other indications for which there is no specific FDA approval but, nonetheless, commonly accepted and used -- leukocyte reduction being used in such settings -- was to reduce the incidence of CMV and also HTLV or, in other words, reduce the incidence of cell associated viruses, and also reducing the incidence of alloimmunization.

From a clinical standpoint, although there was insufficient data for this to rise to the level of FDA approval, data is accruing and potentially it will receive FDA labeling approval in the near future, and there is moderate -- and also these indications in terms of relative clinical importance might be stated as being of moderate importance.

Now there are a slew of other controversial indications for which there is little scientific data to conclusively recommend leukocyte reduction, and those include immunomodulation, the storage lesion, the transmission of other infectious diseases, viral reactivation, and possibly the reduction of transfusion related acute lung injury.

Now the first two of these at least have received a lot of public attention, and potentially, if proven to be true, it carries the highest level of

clinical importance for leukocyte reduction. Again, not to say that any of these indications are not important, but in terms of relative scale I believe the controversial indications are actually ones that are really driving the public consensus toward universal leukocyte reduction.

Of course, the potential use against transfusion associated graft versus host disease is not relevant, because we have a more definitive way of preventing that from happening by gamma irradiation.

So this was the summary of the data presented to the BPAC members, and this is the basis on which many of the committee members reached their decision -- I should say probably all of them, with three abstentions, and all in favor of Yes.

In terms of adverse effects, these were also discussed at the BPAC. In terms of reactions that are specific to a particular filter or even a filter lot, only one was discussed, and that was the red eye reaction. This has since been resolved with stopping the distribution of that particular make of the filter.

There are several other potential adverse effects that are more general to leukocyte reduction filters in general, including hypotension, and this is largely associated with bedside leukoreduction rather

than pre-storage, as well as cell loss and hemolysis, both of which is easily tolerated and more than acceptable.

As for adverse effects of leukocyte reduction itself aside from devices that achieve leukocyte reduction, there were none, and I believe in the absence of significant adverse effects and with the charge not to consider costs, the BPAC voted the way they did, despite not having conclusive evidence that leukocyte reduction is beneficial to all transfusion recipients.

So if you expand the BPAC committee vote -- and of course, I made this up, and this is not in any way a formal record -- you might sort of lay it out in terms of a scale: 3+ Yes; 2+ Yes; 1+ Yes; going to 3+ No.

Obviously, people abstaining could not really reach a clear decision and didn't vote either way, but I believe the 13 people that voted yes were probably doing so on a 1+ Yes decision, and this is based on the comments that they provided which explained their rationale. Again, health care costs were not considered at this time.

So how has the public dialogue shaped up since 1998 BPAC? Well, BPAC recommended universal

leukocyte reduction, irrespective of CJD or new variant CJD, and with a charge to not consider cost issues.

Because of the way in which BPAC voted, this issue was not presented before the Transmissible Spongiform Encephalopathy Advisory Committee, and the issue was brought before the PHS Advisory committee in terms of blood availability and costs. However, the committee supported BPAC's recommendations without clear guidance on time frame or how aggressively universal leukocyte reduction should be implemented.

So it is the goal of today's workshop to develop public consensus on implementation issues as to how we might best move forward, given the recommendations that have been derived thus far.

So in terms of an overview, in Session I we will try to lay the ground work once again, just to familiarize everyone in the audience with the scientific issues and clinical issues associated with universal leukocyte reduction.

What does universal leukocyte reduction mean for the transfusion recipient? This topic will be addressed by Dr. Ed Snyder who was also invaluable in shaping the BPAC discussion held in 1998.

That discussion will be followed by Carolyn Jones from HIMA, a representative of the filter devices

manufacturing industry, to make a statement as to the availability of the filter supply in terms of is it possible to immediately implement universal leukocyte reduction if that is the consensus developed today.

In Session II presenters from the FDA will provide some potential regulatory approaches. I will go over some of FDA's current thinking on standards and time frame. Betsy Poindexter from Division of Hematology will also do the same with respect to platelets, and the tricky concepts relating to good manufacturing practice standards, licensing issues and a CBER pilot program will be discussed by Mary Gustafson, and Larry Fenner from the Office of Compliance and Biologic Quality will discuss whether or not the transition period will be laden with compliance issues.

In Session III the workshop committee has invited five U.S. centers to discuss their experience and provide proposals on implementation. The committee has decided to focus on domestic centers as implementation issues must be addressed from the standpoint of specific -- issues that are specific to the United States, keeping in mind some of the reimbursement structures, that reimbursement structures differ in other countries that have already implemented

universal leukocyte reduction.

The five centers invited here today are the American Red Cross, Blood Systems, New York Blood Center, Community Blood Center of Greater Kansas City, and Cedars-Sinai Hospital, as well as America's blood centers.

Lastly in Session IV, a discussion of key implementation issues will be held, and the highlights of the discussion and concluding remarks will be provided by Dr. Harvey Klein of the Department of Transfusion Medicine at National Institutes of Health, who, among the people that I polled, none disagreed that he was the logical choice, and also he is also part of the regulated industry as well as being somewhat neutral, being part of the government as well.

So in terms of actual workshop goals, the ones I listed here are rather slam dunk goals. The fact that we are here ensures that this will happen. We will discuss the U.S. experience to date on universal leukocyte reduction. We hope to exchange ideas on how to best implement ULR and, I think, more importantly than others, provide a forum in which industry guides industry members and, of course, generate the basis for a future FDA guidance.

I'd like to point out one ground rule in

discussion in proceeding with today's workshop. Participants may refer to the following aspects of leukocyte reduction as they relate to implementation of universal leukocyte reduction, but they should not be addressed as primary issues.

Those are cost issues, as this is not the charge to the FDA or for this workshop, clinical risks and benefits as well as scientific principles, as these have been discussed previously and it's really beyond the scope of this workshop.

At this stage, I'd like to go over some more specific goals or I call them key decisions, and I'll simply read them:

Key decision 1 -- and I believe these are the more tricky issues to be discussed today: Should FDA recommend specific implementation criteria applicable to all blood establishments or should FDA provide only the framework within which blood establishments adopt an implementation plan specific to each center?

Key decision Number 2: Should FDA recommend a simple transition period of 12 months or briefer or should FDA support transition periods that are longer than 12 months, which may allow further maturation of cost, clinical and scientific issues?

Key decision Number 3: Should the current FDA guidance on leukocyte reduction be retained for use during the transition period or should the definition and quality control of leukocyte reduction be updated form the current FDA recommendations for implementation during the transition period?

Key decision Number 4, and this is getting a little bit tricky: Should blood centers, if eligible to participate in the CBER pilot program for streamlining licensure, be able to obtain the license for leukocyte reduced blood products by the simple self-certification of compliance with existing leukocyte reduction standards or should blood centers, if eligible and interested, continue to be required to submit evidence of compliance with existing leukocyte reduction standards for CBER review in obtaining the license to ship leukocyte reduced blood products across state lines?

Lastly, key decision Number 5: If a blood center already licensed for whole blood red cells or platelets may self-certify in supplementing its license to include leukocyte reduction, should it be able to self-certify compliance with the existing 1996 FDA memorandum on leukocyte reduction or should CBER write a new pilot guidance for leukocyte reduction under GGP

in order to allow self-certification, although the pilot guidance may not be substantively different in terms of content from the existing 1996 memorandum?

So I believe those are five relatively tricky issues that will come up in today's discussion that, hopefully, will shape the discussion toward how to best implement ULR. Once again, I would like to thank the entire workshop committee in making today's workshop possible.

At this point, I'd like to introduce Dr. Ed Snyder from Yale. He is a speaker who requires no introduction and who will address the issue of leukocyte reduction, blood quality and the transfusion recipient.

DR. SNYDER: Thank you. Sorry for the delay.

Good morning. I'd like to first thank the FDA for inviting me to make this presentation. It's a somewhat difficult presentation, since so many in the audience are quite sophisticated in this area.

So what I plan to do is to cover in my usual fashion all the material I can in the allotted time, but going over those areas which are fairly common quickly, just to mention them for the sake of completeness, and dwell more on some of the more

interesting areas that, I think, we should discuss with leukoreduction.

I want it to be clear that some of the comments I'll make as we go through this are my thoughts and how I feel that personally that leukoreduction is clearly a safer and a better product and that the time for implementation for this is now. I'll try to rehash many of the medical and clinical indications for these products.

As you can see here, we have a fairly large number of types of white cells that need to be removed, and we remove them for various reasons, as we are aware.

Filtration started, again, in 1938 with Fantis in Chicago removing basically clots. We then moved fairly rapidly ahead to microaggregate filtration to remove debris, spurred on by the work of Dr. Swank whose filter is over here, and a variety of other filters.

This particular filter, as I've mentioned, has a priming volume of 200 ml. This did not survive very long. These filters were very useful for decreasing the microaggregate debris, and were used in treating respiratory distress syndrome. It turned out that was more likely to be due to infection and

hypotension than to microaggregate debris. But these kinds of pictures were very histrionic, and certainly impressed a lot of people with the removal of debris.

The field moved on quickly, however, to removing individual white cells, and that became clearer as we developed more understanding of immunomodulation and what was happening with cells, that it wasn't just removal of granulocytes and debris but actually white cell leukocytes, lymphocytes and various types. So the ability to remove them developed with the so called third generation leukoreduction filters.

We now have indications for leukoreduction, which are seen here. Some of them are more well accepted than others, and I will go through some of the strategy that -- stratification that was presented at the BPAC meeting a year ago in September.

So I think, although there were scientific indications, from my perspective what has spurred the field to move forward very rapidly has been the concern about transmission of new variant CJD, and I think most people would agree that that probably is not related to leukoreduction, but it has been, I think, the political motivating force in various countries around the world and I think, to some degree, the concern about

transmission has spurred the industry to move forward for reasons which I think are beneficial for the conditions we're going to talk about, not necessarily for that.

This slide I wasn't going to show, but I actually think it's still current. Those of you who go on the AABB Web and look at the sig cites realize that there are thought leaders on that site that actually feel that leukoreduction should not be mandated.

There are no single noncontroversial indications. I can't think of a single one -- perhaps CJD, but there are people around the world that would quibble with that as well. So I think we are really looking at not one single indication but a group of indications which, taken together, have the sum of the parts being greater than any individual one and, certainly, putting together as a whole I think that each individual indication has certain weight, but when linked with other ones, gives you an overwhelming indication for leukoreduction.

So let's look at the level of consensus. To decrease febrile transfusion reactions: I think pretty much everyone agrees -- many people agree that there is consensus that this will occur. We now know why this is the case. Not only does it remove the

cells, but it also removes the cytokines before they are formed by removing the cells.

Decrease the incidence of HLA alloimmunization: That's because of removing dendritic cells. To a large degree, that will decrease, although not completely eliminate, the HLA alloimmunization. There are data from that. Everyone says, well, there's no data that leukoreduction is needed. There are data for febrile transfusion reactions. There are data which we'll show very briefly for HLA antibodies from the TRAP study.

Decreasing cytokine generation with pre-storage leukoreduction: There are data for that, that if you remove the leukocytes prior to storage, there are fewer cytokines generated.

The decreased generation of platelet and granulocyte microparticles: There's also data on that.

So this slide just goes back to an abstract that Linda Chambers and her group published in 1989 in Transfusion which basically said that leukoreduction filters really didn't have much of an effect on febrile transfusion reactions. With the unfiltered group and the filtered group, 20 percent reaction, 14 percent in the filtered group, not felt to be statistically significant, that only three patients really had any

impact on the overall difference.

This was, we now realize, due to the fact that they were looking at beside filtration. They were looking at products that had been stored and cytokines that had already been generated. We thought initially that, if you remove the cells, that the febrile reactions would disappear, when in reality, as has been shown by Nancy Heddle -- and I'll show that in a second -- it's the cytokines that apparently are more of a problem. So that was actually correct.

This slide -- By the way, I should have a disclaimer. I do have fee for service contracts with Baxter and Terumo and Pall. I do not own any stock in any of these companies, and I am on advisory boards for Baxter and Pall but, as I say, have no financial interest in the companies.

This just is a slide which was taken from Baxter, which was data that we had generated, that if you pre-storage leukoreduced platelets, you do not have the production of, in this case, interleukin 8, where in nonfiltered units you do see production of various degrees of interleukin 8 as an example of other cytokines.

The importance of this slide, I think, is that there's biologic variability, and I'll come back

to biologic variability when I get to the immunomodulation aspects of things. Not all people are the same, certainly when it comes to these kinds of reaction and generation of these cytokines.

This paper by Nancy Heddle, which is in a now classic New England Journal where she took platelets and divided them into the platelet for Supernatant and the platelet rich infernatent and infused them into the same individual separated by a period of time and looked for febrile reactions, randomizing whether the platelet for plasma was first or the cells.

There was no reaction in 30 of these paired transfusions. Plasma only reactions occurred in 20. Cell only reactions occurred in six, and plasma in cells to eight. The conclusion was that the cytokines that were secreted into the plasma were more important than were the actual cells in producing the febrile reactions, which fits in with what, I think, current status is, and we are still hearing variations on this theme today. That, I think, is pretty well agreed.

This is the also classic Mo Blajchman studies on the New Zealand rabbits where he evaluated leukoreduction prestorage, post-storage and non-leuko depleted, looking at the refractory rate. Again, the

highest refractory rates in the non-leuko depleted, the least in prestorage, and the interim in the post-storage leukoreduction for the rabbit model.

When he just infused plasma into these animals looking for the same things, -- again you are all familiar with this -- stored plasma had a 61 percent refractory rate, and fresh plasma only 16 percent. So the data was that there was something in the stored plasma that was having an impact on the rate of reaction.

When white cells -- reduced red cells were compared with plasma depleted red cells, the refractory rate dropped in his animals from 29 percent to zero. The implication of this, as we are familiar, is that microparticles were present in the leukoreduced red cells that were getting through the filter.

This slide just shows you what kinds of these particles might look like, the fragmentation of the membrane. This is in a granulocyte. It's not related to the neutrophil which would have the Class I and the Class II sites on them, which would be more germane, but this picture -- you actually get a stronger visual impact. So I chose that.

A paper by Ramos showed that these cell fragments will go through the filters pre- or post-

filtration, but there is an increase in the amount of these fragments over time. The presumption is that you are infusing Class I and Class II antigens. You are also -- There's also antigen presenting cells in the recipient, which can present the antigens to produce antibody against Class I and Class II, resulting in alloimmunization.

So the idea would be for quality purposes pre-storage, leukoreduction would appear to be the best way to go, decreasing cytokines, decreasing any -- minimizing, rather, cytokine production, minimizing HLA alloimmunization.

The TRAP trial concluded that leukoreduction by filtration and UVB irradiation was equally effective in preventing alloantibody mediator fragments. So there are data there.

Use of leukoreduced single donor versus leukoreduced random donor was of no added benefit, and the slide is here taken from that article by Schlichter and her co-workers, the control group showing the highest degree of refractoriness, and the three types of reduction, alloimmunization suppression, either UVB or filtered concentrates of filtered apheresis products showed a similar lower level.

So I think there are data that

leukoreduction is beneficial to decrease the incidence of alloimmunization.

What about other levels? Well, decreasing HIV activation post-transfusion was thought to be a really good idea. There was information presented, although not formally, at the AABB meeting that the results of the VATS trial which is sort of a leaking of information, if you will, a leaky VAT, is that the use of leukoreduction did not appear to be any different from the control arm as far as p24 antigen and clinical response.

I haven't seen the data. We need to be able to evaluate it, but the rumors, unsubstantiated rumors, are that the HLA -- that leukoreduction did not appear to have a beneficial effect for HIV transmission, prevention of it or decreasing reactivation of HIV.

This was based on Dr. Mike Busch's paper where he added white cells to cells in culture and looked at the degree of p24 antigen that was secreted into the Supernatant.

CMV transmission, however, is an area where people seem to have a general agreement. Now the key paper again for the millionth time is Dr. Bowden's paper, which comes to basically this line over here for

the secondary analysis of patients on Day Zero to Day 100 with the intention to treat CMV disease only.

There were no people in the seronegative group, in the filtered group six, and six versus zero was significant, less than .05, whereas in the 21 to 100 primary analysis zero versus three did not reach significance.

This sort of sat around for a long time, but then the industry that was transfusing leukoreduced blood products under cGMPs was not reporting an increase incidence of CMV in the recipients, transplant recipients.

I think now there's a general -- Although there has been no additional formal study, there is now a general feeling that under cGMP purposes prestorage leukoreduced blood products are considered to be CMV safe, and many centers around the country are using it. We are using it at Yale, including for our allotransplant patients and, knock on wood, have not seen concerns, as are many other major centers around the country.

Not everyone follows this. Many places are using it for all but allotransplant patients, but there seems to be, by dent of the numbers in the field, an affirmation that Bowden's study was probably correct in

that CMV safe is a real product that's leuko-depleted under cGMP conditions.

There is a high level of consensus that leukoreduction will not prevent post-transfusion graft versus host disease. This is a paper by Okahoshi, which was in Transfusion in 1992, which basically showed an individual who had received platelet concentrates that were leukoreduced but not irradiated, and developed post-transfusion graft versus host disease.

Although theoretically you might be able to get the numbers down to prevent graft versus host, I think most prudent physicians and, certainly, most attorneys would agree that it's best to use gamma radiation at the indicated dose with the FDA guidance to prevent graft versus host disease.

Whether or not the upcoming psoralen inactivation materials, psoralen or riboflavin or other types, will be able to give you the same effect has yet to be shown formally, but it is possible that there may be other ways of inactivating white cells. But for now, leukoreduction is not considered an indication to prevent graft versus host disease, in my reading of the literature.

Again, high level of consensus that use of

leukoreduction to prevent transfusion transmitted new variant CJD is not a concern. So I won't spend anymore time on that.

Now we come to areas that are of much concern, which are areas where there's low level: Removal of bacteria, tumor growth, immunomodulation, post-op infection, reprofusion injury, and response modifiers.

Suffice it to say that removal of bacteria from blood is not an indication which will likely to see the light of label copy. There are data in the literature published by our group as well as others, a lot from the Red Cross, Steve Wagner, that you can remove a large number of bacteria from white cells -- from units of blood.

Whether the leukoreduction is because the filter is removing the bacteria, the filter is removing bacteria stuck to white cells or the filter are removing bacteria ingested by white cells may all be correct. But there are so many strains, and there were examples of various spiked bacterial experiments where they proliferated -- the bacteria proliferated, regardless of leukoreduction, especially with gram negatives, that it is not likely to occur.

Is it likely that leukoreduction will

enhance the degree of bacterial safeness, if you will? I think probably that's true, but it will be hard to show that data, but it would be another benefit to be achieved if leukoreduction were implemented on a universal basis. So there's low consensus, but there's good data that it is beneficial, to some degree.

Let's skip this, because we're going to get back to that in some detail.

Prevention of reprofusion injury -- Well, let me just go to this. Biologic response modifiers: There's good evidence again from our lab and others that some blood filters will remove some response modifiers, such as interleuken 8, rantes, the complement factors, primarily because of electrostatic interactions because of their positively charged molecules being ruled by negatively charged filter. But many of the negatively charged response modifiers such as the interleuken 1 and IL6 and TNF alpha are not removed. It's an electrostatic interaction, and the more of the product that's filtered, the less the efficiency of removal. So it's really not an indication.

As far as reprofusion injury is concerned, oxygen derived free radicals are certainly associated with the return to profusion of an ischemic organ. If

you cross-clamp the aorta or do an organ transplant, there are receptors that are generated on the epithelial cells and other types of cells.

White cells become activated, and various agents are released, including oxygen free radicals, which will cause damage in extant infarct areas. Is that an indication for leukoreduction? Not unless you have a leukoreduction filter in the circulation, which is not practical, obviously.

So that you may remove the white cells from transfused products, but the granulocytes are not very viable in these products, to begin with. So there really is not much indication, although there are some very interesting data from the surgical literature showing there may be some benefit to this.

In addition, there is a paper by Dr. Massberg in Blood 1998 which shows a vessel which is profused normally, and here's a vessel that was released from an ischemic interaction. What you see lit up here are platelets.

The purpose of this paper was to show that reprofusion injury can be due to platelet activation as well. So it's not just -- Even if white cells removal did play a role, platelet activation could cause reprofusion injury, in addition. So this again is not

a really -- is not a well accepted, by any means, indication for leukoreduction but might be some benefit that would be derived, were it to be used.

So let's go and take a little bit of time and look at the immunomodulation aspect of it. This was again another Dr. Blajchman bleed-the-bunny study where he looked at New Zealand white rabbits.

What he evaluated was the effect of syngeneic, allogeneic and leukodepleted allogeneic transfusions on metastases. As you can see here, almost all the rabbits essentially did have metastases, but the median number of metastases was the least for the leukodepleted allogeneic and the syngeneic and statistically significantly differently higher for the higher allogeneic.

So the implication was -- and there have been lots of studies which show -- seem to show that leukoreduction prevents metastases, recurrence of metastases or the development of metastases, recurrence of tumor and decreased post-operative infection.

One of these studies by Lon Jensen showed a statistically significant drop in the number of abdominal wound sepsis, with unfiltered whole blood being the highest and filtered whole blood being very low, again very small numbers. Some of the other

things that were looked at did not reach statistical significance, but this is an example.

There are lots and lots of papers. I'm not going to go over them. Some show that there are benefits of leukoreduction in preventing tumor recurrence. Others show that there are not. The question is -- Then we have meta-analyses which say maybe, and that's my final answer.

There are people who strongly feel it's helpful. There are people who strongly feel it's not. What I feel the time is right is to take a look at the basic science and what data is there that leukoreduction has any impact at all on this or is this just a bunch of clinical trials that have fun things to know and tell, but really don't give any kind of a cohesive picture.

This is one of my favorite slides from Jensen's paper showing that unfiltered whole blood -- You had a 17 day length of stay, and only 11 days with filtered whole blood. So you could actually drop the length, median length of stay, almost by 50 percent total bed days here. If you didn't get transfused it was 967. If you did, it was only 537, but there were more patients in this group, to be fair.

This again showed total bed days were less

in essentially a comparable group of people here. So is filtration that wonderful? Can we decrease length of stay. Are we going to wipe out the blood bank by having to pay for all these filters, but the hospital will benefit by having decreased length of stay and it will have a better bottom line.

Well, we're not going to discuss that. We're going to discuss some of the science. There was a paper by Dr. Ghio -- the senior author was Francisco Pupo -- in Blood earlier this year on immunomodulatory effects of transfusion.

They wanted to evaluate leukocytes in donor blood having effects of inducing transplant tolerance, accelerating tumor growth, recurrence of tumor growth, and increased risk of bacterial infection. These are the issues that they wanted to address.

They weren't sure of the exact mechanism, but felt that it may involve induction of anergy, anti-idiotypic antibody, mediated expression, cytokine expression imbalances, T-cell clonal deletion, regulatory activity, and various soluble factors. This is what they concentrated on, soluble HLA Class I, Class II, and soluble Fas ligand.

What they showed is here. This bottom panel is soluble Fas ligand. Soluble Fas ligand, as

we'll talk about, is a Type II protein which is secreted and binds to Fas. Fas is a receptor on cells which, when bound to Fas ligand, induces apoptosis and cell death. Okay?

So we have soluble Fas ligand secretion here, HLA Class II and HLA Class I, in washed red cells. This is going up -- red cells that are absorbed for five days, red cells absorbed for 30 days, leukodepleted red cells, platelets, FFP, and serum.

What you can see it that the largest levels of soluble Fas ligand are in 30 day old red cells and in platelets with very low levels in washed five-day-old red cells, leukoreduced red cells and FFP. That's true also for HLA Class I over here and less so for Class II.

So there seems to be 30-day red cell and five-day stored platelets, the highest levels of these modifiers. So as I say, Fas ligand is a Type II membrane protein which is expressed in activated T-cells in granulocytes. The Fas, also known as CD-95, is expressed on tissues and, when they bind, apoptosis will develop, cell death.

This binding can result in a cloned deletion of T-cells in the periphery and a down regulation of cytotoxic T-lymphocyte activity, and

soluble Fas ligand is at serum and reported to be high in hematologic tumors, all very well and good.

Well, this is what apoptosis is all about. The cell begins to undergo apoptosis by pulling -- I will bring this back to leukoreduction, if you bear with me, in a minute or two. This is getting it to some of the basic science, and I want to make sure everyone gets at the same level here, to the best of my ability.

The cell begins to pull away, which is an apoptotic cell, and undergoes a series of changes resulting in nuclear blebbing and then cytoplasmic blebbing, and this is not necrosis, but this is a program cell death. The cell then gets destroyed, and it gets eaten up by its neighbors.

This is a slide showing the exact -- what the cartoon showed previously, with cytoplasm blebbing and so forth.

Now this will occur. This is a slide taken from one of the catalogs from one of the companies that makes these reagents. What you see here are a bunch of receptors, and then you see here a bunch of ligands which are binding, and among these is -- here's Fas, and here's Fas ligand. So this is a T-cell, and here's the Fas receptor.

When Fas ligand binds to that Fas receptors, a series of quite complicated metabolic processes occur with CAS phases and DCLX and BCL2, a whole variety of things we're not going to go into, but results in cell death. The cell is told it's time to die.

Now you can imagine a scenario where you have cytotoxic T-lymphocytes which are suppressing tumor -- this is quite simplistic, but a potential scenario -- and then you infuse red cells or platelets with soluble Fas ligand, which binds to those Fas receptors on those T-cells and induces apoptosis, thus releasing the tumor from inhibition, and you get growth of tumor.

This could be one possible scenario for why some people find that there is an increase in tumor metastases with transfusion, but if you leukoreduce, prestorage leukoreduce and then prevent the Fas ligand from being formed, there won't be that kind of inhibition.

Again, this may be very simplistic, but it gives us a way to get into the science of this. Now, obviously, there are multiple receptors, and I want you to especially be aware of this one, DCR-1 and DCR-2 which have a transmembrane piece, which are also

involved. These are called decoy receptors. We'll talk about that in a moment.

So I think you understand how finding Fas ligand production in blood products may have an impact clinically on potential effects with tumor growth.

Now what's the evidence that the Fas ligand is actually active? Well, this is a way of looking at degree of apoptosis. Here's a cultured medium, and here's DNA content of about 40.

If apoptosis is occurring, it's going to become less. There's going to be a shift to the left in the curve, and this is a positive control. Seventy-five percent of the cells involved which are Jurket cells, which are T cells that have a Fas on the surface. So here's a positive control where you've stimulated the Fas and you have apoptosis occurring, because there's a movement from this area to the hypodiploid side, 75 percent.

Red cells stored for 30 days, the Supernatant, gave you an 89 percent degree of apoptosis in these Jurket cells, implying that the Fas ligand present in these 30-day stored red cells were active, because it induced death in 89 percent of these Fas cells. Five-day-old red cells only gave you 11 percent. There's a small peak here. Washed red cells,

12 percent; leukoreduced two percent; platelets, 31 percent in this peak; and fresh frozen plasma about 10 percent.

So there's evidence that at least in a Jurket cell model you can get apoptosis occurring. Also looking at the MLR response, what this showed is that in cells where you got a normal MLR response, looking at the very top square over here -- by showing the amount of radioactivity present; this is normal. If you then added to this MLR reaction the Supernatant from a 30-day-old red cell, it obliterated it completely, and similarly for platelets.

This is a normal reaction. If you added the Supernatant of a five-day-old platelet, in the triangles here, you obliterated it. Whereas, adding FFP and leukoreduced -- plasma from leukoreduced platelets in red cells, you did not get deablation, which would be down over here.

So what this is showing is these are active molecules, at least in an in vitro assay. Okay. So that's all well and good.

So what this means is that both soluble HLA Class I and Class II can modulate immune function, can bind to their ligands and inhibit or stimulate apoptosis. This could lead to immune tolerance or

activation. We'll skip through some of these.

The main findings were that there are elevated concentrations of soluble Fas ligand in some blood components, primarily 30-day-old red cells and platelets. The level is proportional to the amount of leukocytes. The levels are proportional to the length of storage. They are functional, and it is believed that these are shed from leukocytes during storage.

So prestorage leukoreduction would inhibit this. Well, we still need to link this to something, and I'll show you what that linked to right now.

There's a paper by Dr. Pitti and a whole slew of people -- this is my own way of not having to write 75 names; the senior author is Dr. Avi Ashkenazi from Genentech -- entitled "Genomic Amplification of a Decoy Receptor for Fas Ligand in Lung and Colon Cancer."

What they found was there was another decoy receptor which they called DCR-3 which did not have a transmembrane piece and was secreted. This material, DCR-3, is a decoy receptor, and that it binds to Fas ligand and inhibits Fas ligand induced apoptosis.

They found that DCR-3 was produced in the tissues in half of 35 primary lung and colon tumors they studied. So if you have a tumor which is

secreting this DCR-3, this decoy receptor, binding Fas ligand, it could block the apoptotic signal and enhance the cancerogenicity, if you will, of that particular tumor. It could be resistant to apoptosis and, therefore, more likely to enhance tumor growth.

This suggests that certain tumors may escape Fas ligand dependent cytotoxic attack by expressing this decoy receptor that blocks the Fas ligand. This could -- It would be one explanation why studies that purport to show colon cancers having -- there's an effect in colon cancer metastases of using blood transfusions. Some have results that are positive, and some are negative, because not all tumors are the same.

What we consider to be colon cancer and a colon cancer and colon cancer may be different, and we have to get more sophisticated analyses to see if these tumors are producing receptors like DCR-3 plus a lot of others.

Therefore, it may be, in a sense, garbage in, garbage out. We're looking at what we think is a uniform group of cells. In reality, they are much more sophisticated. In our own naive way we're thinking, well, you leukoreduce, and that's going to cure cancer. It doesn't work that way, necessarily.

These are some of the mechanisms which, hopefully, can be developed through the NHLBI and so forth to study this on a scientific basis, knowing that these response modifiers are produced in blood products.

So the answer to is leukoreduction going to prevent tumor growth, is it going to prevent sepsis -- the answer is we don't know, but there is a linkage, and there may be some justification for why some studies appear to show a positive result and other studies don't.

So it's still a low indication, but I think it's one of the most exciting ones, and ones that will be discussed at a conference that we're going to be having in March, that you're aware of.

In addition, there is some work that Dr. Harold Merriman published many years ago looking at other aspects of anergy. Not only does leukoreduction seem to prevent the -- take out the antigen presenting cells, but he showed that if you stored blood over 13 days, the secondary signal, the B7 signal, did not appear, and there is some additional data now that just came out in Blood a short while ago showing that blood that's been stored for a period of time does not stimulate alloimmunization but actually may produce

anergy.

So leukoreduction removes a lot of these concerns, but there are certainly aspects of immunomodulation which are far more important. I think, if we're going to get the maximum benefit of leukoreduction, it has to be prestorage, and bedside leukoreduction is not going to address these concerns and, certainly, by the time you start leukoreducing, the cytokines and the response modifiers may already be present. So I think that addresses a quality issue.

There is also a paper by Dr. Jon Semple that was in Blood in 1999. Extreme leukoreduction of major HLA complex Class II positive B cells enhances allogeneic platelet immunity. This paper purports to show that, if you leukoreduce excessively, you may actually stimulate alloimmunization rather than decrease it. It decreases to a point, and then after a certain level you start to get an increase in alloimmunization, sort of a paradoxical effect.

So there's lots of areas. I don't think we're going to get to the degree of leukoreduction that they're talking about here, but it was just another interesting aspect, that all leukoreduction may not be beneficial, depending on the degree.

There are data in the literature that,

whether it's leukoreduction by filtration or process leukoreduction, you may get different amounts of leukocyte subsets. There are some people that live and die by these concepts and say that there's far too many granulocytes in the process leukoreduced products.

I think, generally, many people feel that, if you leukoreduce to the same degree, that the effects are similar. Some people quibble with this. More data are needed, but these are some of these types of data showing that process leukoreduction does give you a slightly different subset analysis, and the implications of this have not been shown at all, as far as I know, in the literature.

There was a paper which -- This was a Xerox which I made a slide of -- showing that the good news is that, if you leukoreduce blood, red cells and platelets, you do not fragment the white cells and release prions that may be present in these products, resulting in the spread of CJD. This came out in the British Journal of Hematology earlier this year.

It is an example of people looking for concerns in areas I didn't even think was a concern. I don't think this is a good indication for leukoreduction.

Kaplan-Meier plots to look at whether the

leukoreduction or not had an impact on leukemic outcome of a patient with leukemia, patients with leukemia -- This is their Kaplan Meier relapse resurvival, whether they received filtered blood or leukoreduced blood -- Sorry, nonleukoreduced blood or leukoreduced. There was really no difference between the two. So leukoreduction does not appear to have an impact on survival from AML.

Are there adverse effects of leukoreduction? Yes. We are well aware of the bradykinin issues and the simulation of bradykinin in some situations by some types of blood filtered media that may have a negative charge, with the potential enhancement of the bradykinin that's formed by the inhibition of angiotensin converting enzyme or kininase-2, and there are data for that.

This was a paper by Dr. Shiba in Transfusion '97, which showed a maximum increase in bradykinin and decreasing amounts of ACE due to the addition of ACE inhibitors. The r squared of this is about 36 percent, which means that there is a one-third -- One-third of the change in the y axis is explained by a change in the x axis.

That's a very low level, and not everyone agrees on the way bradykinin is measured. There are

lots of questions. The point is that this was enough, however, for the FDA to issue a medical alert that bedside leukoreduction can produce hypotension. This was in May of 1999. Rapid onset can produce respiratory distress and shock.

It resolves when the transfusion is discontinued, and since '94 80 out 20 million leukoreduction filters have produced this. Is this a major health scourge? I don't know. We're presenting the data, and you can decide on scourges at lunch.

The FDA doubts that this is due to ACE inhibitors or negative filter media. However, this is sort of like Y2K. There will be no Y2K problem, but get extra flashlights and just don't be in an elevated building or in a subway when the clock strikes midnight.

They recommend watching for a decrease in blood pressure with leukoreduction filtration, flushing, stop the transfusion, and use prestorage or in-lab leukoreduction filtration. So again, this is sort of where the state of the art is for this.

There is also questions about whether -- this is a paper by Willis -- whether fresh frozen plasma should b leukoreduced. The data are that there are bags which have greater than five times 10^6 white

cells in it of fresh frozen plasma, leukocytes and lymphocytes that may survive this. Whether that needs to be leukoreduced also hasn't been fully evaluated at all.

This slide actually is from The New England Journal from years ago. I used to think this was a patient. This is the doctor. This is not the patient. The doctor -- This IV pole was on loan.

What this means is that this is a cost issue, which I'm not going to get into, other than just to show this slide which will not go away. It continually pops up.

So what are my thoughts on universal leukoreduction as we get to the new millennium? That, number one, they are Y2K compatible, although often they stop running for no apparent reason. So maybe they are not. Who knows?

They are increasing in popularity. Our hospital administrators -- and this means, may they all live and be well -- are accepting leukoreduction as a standard of care. The Red Cross, America's blood centers, and others are converting generally, and probably will drop the cost as the volume of products increases. This is economics.

If this is true, it could decrease length

of stay. If all those things that we heard about, decreasing length of stay and decreasing tumors work, it may actually be beneficial. So they actually could end up paying for themselves.

This will benefit the hospital, but not the blood bank or the blood transfusion service, which is a cost center. One benefit, if you consider universal leukoreduction as CNV safe, there is some financial savings to be considered in that regard.

The switch to universal leukoreduction would decrease inventory problems, so you don't have multiple parallel inventories, which certainly we found to be helpful. My belief is that nonleukoreduced blood products will go the way of fresh whole blood.

Our institution was able to convert relative small dollars, which we can talk about at another time, and we did this by going to the medical board, presenting the case, and then the medical -- the transfusion committee first, then the medical board, and now we're solely implementing and trying to do internal reassessment of our budget.

So lastly, even if universal leukoreduction is in place, according to the CFR 606.122, instructions to use a filter in the administration equipment, you still will need to use a 170 micron filter. That is

still a requirement, and the CFR is unlikely to be changed in this regard. This is just an FYI.

So are we ever going to get to Happy Valley where everything is wonderful? I don't know. We have a long way to go, but the data, I think, I tried to summarize for what you knew on leukoreduction and express some of the changes that are occurring in the immunomodulatory and the septic area where I think some really exciting science is going to be generated.

So I'll stop there. Thank you very much.

(Applause.)

CHAIRMAN LEE: Thank you, Dr. Snyder.

In the way of questions, unless it's really a burning question, I would ask the audience to actually just jot them down and hold them until we get to the panel discussion. Many of the questions may be answered during the course of people's presentations, and also I think it would make for a tighter conference if you would just simply jot them down and hold them.

Our next speaker is Ms. Carolyn Jones from the Health Industry Manufacturers Association, who is really is tasked with a difficult job of representing all of the device manufacturers. I really thank her input in contacting all the individual manufacturers, developing a consensus stance for today's presentation.

MS. JONES: As Dr. Lee indicated, I'm here today representing the Health Industry Manufacturers Association. HIMA is a Washington, D.C., based trade association and the largest medical technology association in the world.

HIMA represents more than 800 manufacturers of medical devices, diagnostic products and medical information systems. HIMA's members manufacture nearly 90 percent of the 62 billion of health care technology products purchased annually in the United States and more than 50 percent of the 147 billion purchased annually around the world.

Some of our members manufacture products that contribute to the national effort to improve the safety of the nation's blood supply.

I just wanted to take note that today's presentation will also include information from the apheresis manufacturing community. It's not just the filters. We decided that we would sort of like to provide the information on the broad landscape rather than just what the filters can do.

I'd like to thank the FDA for inviting me today to present the industry perspective on the ability of the medical device industry to meet the demands that will be imposed by CBER's anticipated move

to universal leukoreduction of all cellular blood and blood products intended for transfusion.

Leukoreduction is being used increasingly to prevent transfusion reactions, alloimmunization, disease transmission, and to reduce health care complications while on transfusion. Leukoreduction can be accomplished by various methods, including the use of dockable systems, in-line red cell systems, in-line whole blood systems, and by apheresis.

Interest in these various methods of leukoreduction has increased as the blood supply has come under increasing scrutiny around the world. Leukoreduction is now mandated in at least nine countries, and a number of other countries are considering mandating it, with implementation processes that have ranged from six months to two years.

The shorter implementation times are recent initiatives in countries having more experience with the practice of leukoreduction or in countries that have sort of benefitted from the experiences of others.

We would like to note that none of the countries where universal leukoreduction has been mandated or implemented collect the number of units collected here in the United States. The number of units collected range from 100,000 units per year to

2.3 million per year.

Just to provide some idea of how leukoreduction is growing, one year ago there were an estimated 7 million leukoreduced blood units provided worldwide. Currently, worldwide there are an estimated 10 million units provided annually.

As Dr. Lee indicated earlier in his presentation, in September 1998 the FDA's Blood Products Advisory Committee voted unanimously for leukoreduction of all cellular blood products. By December 1998 leukoreduction in blood centers was already expanding, such that 10-17 percent of the nation's supply was leukoreduced. Of that, bedside leukoreduction was the dominant method and was performed twice as often as prestorage leukoreduction performed in a blood center.

Six months later in July of 1999, the rate of use had climbed another 30 percent, so that some 25 percent of the nation's supply was leukoreduced. At this time, 60 percent of the leukoreduction was being done not in a hospital but rather at freestanding blood centers. The rate of leukoreduction continues to grow about five to seven percent per month.

In general, bedside leukoreduction in hospitals is declining, but is regionally variable as a

factor of blood center policy. We will no doubt hear from the blood collection community present that currently blood centers are voluntarily practicing leukoreduction in a range of 15 percent to some 100 percent.

Methods for leukoreducing blood components at blood centers are dependent on the center's experience, manufacturing costs, manufacturing operations. These operations vary from center to center, creating user preferences based on ease of use, quality control, and facilities' capabilities.

This is particularly true for the type of filter or filter set used by the different centers. The question now becomes what's going to be the time frame for implementation of the requirement for 100 percent leukoreduction in the United States?

If we assume, based on current trends, that one-half the blood transfused in the U.S. in the year 2000 will be leukoreduced, we can attempt to make some estimates or some predictions about utilization.

We believe that 50 percent of the red cells transfused will be leukoreduced, and that the trend toward prestorage leukoreduction will continue. Next slide.

An even higher percentage of platelets will

be leukoreduced in the upcoming year. We estimate about 68 percent. This estimate is even higher for single donor platelets where greater than 95 percent will be leukoreduced. Next slide.

Fresh frozen plasma has not had visibility as a blood component requiring leukoreduction. To date, there are no standards defined and, therefore, it's difficult to measure the quantity today and in the future. Next slide.

This move toward universal leukoreduction in the United States has not been lost on manufacturers, who have already begun to expand manufacturing capacity. Typically meaningful expansion in capacity requires six to eight months for add-on leukoreduction systems, 12 to eight months for integral collection systems, and six to 12 months for transition to whole blood platelets to leukoreduce single donor platelets collected by apheresis.

Most manufacturers began the process of expanding manufacturing and production capacity at or before the 1998 FDA Blood Products Advisory Committee vote for universal leukoreduction.

At this juncture, that expanded capacity is today becoming available. Realizing the need through discussions with blood providing organizations,

manufacturers have already begun allocating more resources to meet the needs of universal leukoreduction.

While supplies are still somewhat limited, due in part to some Y2K hoarding outside of the United States, by February 2000 we expect capacity to meet the current rate of expansion, which is about six percent per month. At six percent compounded growth, the U.S. will double to 50 percent leukoreduction in about one year, and achieve universal leukoreduction by December 2001.

We believe that manufacturers can confidently support this rate of utilization. What is not included in this equation and what is not a manufacturer's issue is the need for the blood banking community to address facility changes, process implementation and validation, licensure, blood component inventory management, and reimbursement issues that are an integral part of determining the timing of any mandated leukoreduction initiative.

From our perspective, these issues must be addressed to ensure that our customers have the resources to accomplish this move. It should be a well coordinated effort and cannot happen overnight.

The FDA must consider expedited review of

biological license applications submitted by the blood banking community for leukoreduced product approvals in order to facilitate any move to universal leukoreduction. Additionally, consideration must be given to who will pay the increased cost of leukoreduced blood components, given the overall emphasis on health care cost containment.

Current reimbursement coding is out of date. It does not adequately address the spectrum of available blood products, leukoreduced or otherwise.

Several options for leukoreduction are available to blood centers and hospitals, including the dockable systems and the in-lines and the whole blood systems, as well as apheresis. Each method or process has its own set of advantages and disadvantages, which we will not discuss at this time.

The red cells are leukoreduced by filtration only. The filtration options include the in-line, the red cell in-line, red cell dockable filters, again each having their own advantages and disadvantages.

We expect a natural utilization mix of 50 percent add-on and prestorage systems and 50 percent integral leukoreductions in the collection system. Red cells again can also be obtained by apheresis, and then

filtered, providing another option.

Single donor platelet leukoreduction is accomplished either as part of an apheresis separation technology or, alternatively, post separation filtration. Whole blood derived platelets are either in-line filtered or a separate filter is connected after pooling.

FDA has not established a regulatory standard for leukoreduced plasma. However, in-line and dockable filtration methods, as well as apheresis techniques, are available to accomplish leukoreduction. In light of this, CBER should review the need for standards for leukoreduced plasma.

Additional options may be available in the future. As such, HIMA believes that the FDA should not mandate the method or means of leukoreduction. It should be up to the blood providing agency or organization to develop or decide on the type of process that is most appropriate for their institution.

By this, we mean dockable systems or the in-line systems, in-line whole blood systems, nonfiltered but verified process controlled apheresis systems should all be available and allowed, as long as the end result is a reliably leukoreduced product.

We also feel strongly that CBER should

continue to review its regulatory process improvements through the device action plan, and CBER should also work to ensure that expedited review procedures and other focus actions help to speed the adoption of the new leukoreduction technologies.

In summary, manufacturers of leukoreduction technologies have positioned themselves to meet the demands of universal leukoreduction. The timing of acceptance and implementation of 100 percent leukoreduction by the medical community and by the blood centers are the drivers of the manufacturers' capacity.

A responsible approach to leukoreduction, universal leukoreduction, involves a process like this workshop and industry alignment on the issues and timing. We do need to work together. This meeting is an excellent catalyst, and we are grateful to all participants.

We in industry look forward to working with the FDA and the blood banking community to achieve universal leukoreduction. Thank you.

(Applause.)

CHAIRMAN LEE: Thank you, Ms. Jones.

This is a rare situation in which we are approximately five to ten minutes ahead of schedule.

So we will go ahead and break early, but if we could reconvene at promptly 10:20 to begin the next session, that will probably be good for the thoroughness of the remaining workshop.

(Whereupon, the foregoing matter went off the record at 9:58 a.m. and went back on the record at 10:21 a.m.)

MR. HOLNESS: Thank you. I'm Leo Holness. I'm a medical officer at the Blood and Plasma Branch of Division of Blood Applications. I'm going to moderate Session II of the workshop, and I'm sure this is the session that you've all been waiting for, the regulatory approach of FDA to the implementation of universal leukoreduction.

Our first speaker will be Dr. Jong Lee. As Dr. Epstein mentioned, Jong heads our Blood and Plasma Branch at CBER, and he will speak on the revised guidance for whole blood and red blood cells. Jong.

CHAIRMAN LEE: Thank you, Les.

During the break, I received a few questions about the possibility of copying some of the what I call the key decisions, so that it will be available to look at while they're conducting discussion.

We did not do that, because when the panel

session opens, what I plan to do is project each one of those on the screen and have it projected as the discussion unfolds. So we'll probably spend about ten to 12 minutes on each point, barring that we stay on schedule.

So with that as a brief remark, as people start to trickle in, I'll begin my next presentation. Just as a comment, although the title as currently printed is "Revised Guidance on Implementation of ULR, FDA Expectations for Revised Guidance of Whole Blood and Red Blood Cells," it's really more of FDA expectations in a general way that are not necessarily restrictive to whole blood and red blood cells but potentially applicable to platelets as well.

So you might also think of it as sort of a general FDA expectations as to specific. Also, I have to point out that this is not the FDA expectation. As you might anticipate, there are many versions within the FDA alone, let alone the industry, as to how to proceed, and I'm presenting one version of that which, hopefully, represents sort of the sum of the diverse opinions that are existing within the agency alone.

Okay. I think most people have gathered back into their seats, and I hear the doors closing. So I'll begin my presentation.

Just to point out, whole blood, blood cells and platelets, which are the key issues, although we've heard references to leukoreduction of plasma, I think we can probably deal with that in the discussion section as to what the FDA should state about leukoreduction of plasma. To me, it's a rather novel thought.

I think it must be fairly easy to achieve leukoreduction of plasma, given standard procedures of centrifugation, but perhaps not. Anyway, the focus remains on the cellular components, whole blood, red blood cells, and platelets, and these are discussed -- these are reviewed -- The submissions for these products are reviewed in basically two areas within CBER.

The whole blood and red blood cells are reviewed within the Blood and Plasma Branch of the Division of Blood Applications and, therefore, I am addressing that topic at this time.

The platelet submissions are routed through the Division of Blood Applications, but the actual review is performed by the Division of Hematology in the Laboratory of Cellular Hematology, and Betsy Poindexter from Division of Hematology will be discussing that aspect in a more specific way.

So there are two presentations on the whole issue. They may come across as two versions, each from the respective review unit, but please keep in mind that portions of each may be applicable to the other, and these are simply alternatives to evolving FDA thinking whenever you notice discrepancies.

We made no effort to come up with a single streamlined view of FDA's expectations, and decided to simply let ideas flow, in keeping with the spirit of today's workshop in developing a public consensus.

What I will go over in the next few minutes is I'll once again point out that the impetus for the universal leukocyte reduction is the BPAC vote, but then make some additional observations about the transition to ULR which often relates back to the BPAC vote, and go over some of the key decisions in more detail.

In my overview this morning, I presented five key decisions, of which I will try to address three as applicable to the actual revised guidance for cellular products, whole blood and red blood cells, for the purposes of this talk.

The key decisions I will be addressing are, as you heard this morning, time frame, the actual implementation plan, and the plan for possibly changing

the QC aspect of leukoreduction process.

Once again, I'd like to reemphasize that the aspect of leukocyte reduction that is of highest clinical importance is actually the controversial indications, and that's the reason we're having so much trouble determining how to proceed. The most important indications are actually the most controversial and, obviously, this happens a lot in medicine.

I have to point out that there is the potential reduction of immune suppression, which hasn't been shown conclusively. There is the potential reduction of the blood storage region, which hasn't been shown conclusively, and there are other potential reduction -- beneficial aspects of leukocyte reduction not listed here.

Of perhaps slightly less importance but important nonetheless is the more accepted indications, reduction of leukotropic virus transmission, reduction of HLA alloimmunization, and then the widely accepted indication, the prevention of febrile nonhemolytic transfusion reaction.

Based on this, BPAC voted 13 to zero with three abstentions, but once again this vote summarizes lack of strong supportive data. However, based on little risks associated with leukocyte reduction, if

any, led to this voting; and also the impact on health care was not considered, and each member of the BPAC committee, when they were explaining their votes, supported a gradual approach to universal leukocyte reduction.

I believe this workshop today is the first step toward that gradual. Some of you may think that this is too gradual. Others think that this workshop is necessary to make sure that we don't proceed too hastily.

Now to turn to some observations, and this is sort of my attempt at summarizing the sentiment reflected in the BPAC voting and the explanation that each BPAC committee member voiced, as well as all the comments I've heard since then.

It seems reasonably clear that, although leukocyte reduction is safe, it remains unclear whether the effect of leukocyte reduction is clinically important for the typical transfusion recipient.

Point number two: Although the transition period presents a unique opportunity to conduct controlled clinical trials that may be otherwise difficult for ethical or practical considerations or to develop public consensus opinions, just the potential of having an FDA mandate of universal leukocyte

reduction, I think, actually removes some of the potential practical considerations of logistics and costs and so forth in terms of conducting such a large controlled clinical trial which is essential, if we are to move forward in generating that data that is supportive of the more important, currently controversial indications for leukocyte reduction.

Without the, quote/unquote, "threat" of such a -- of universal leukocyte reduction being a requirement, such clinical trials are probably not going to happen, but with the anticipation that this is coming in the future, although it's not clear exactly how fast, I think we'll probably foster these trials to happen more likely than if there were no such discussion about them.

In fact, some of these trials have begun already, based on the BPAC vote, well before today's workshop.

The third observation to keep in mind is that the implementation issues differ, obviously, for different centers, and they depend on center mission, the mission of each blood center, the size, and the operational complexity. Although we would like to think that there can be a single FDA guidance to provide as to exactly how each blood center should roll

out or implement universal leukocyte reduction, this appears a daunting task.

The fourth observation: Universal leukocyte reduction should be implemented in a way that maximizes clinical benefits while minimizing risks, and those risks include the potential adverse impact on health care deliver. In other words, you might produce the highest quality blood, but if it results in lower quality patient care overall, then we have defeated our public health mission.

So although we cannot directly consider costs, we are very mindful of the cost issues, and they are always in the back of our minds.

So in terms of what the essence of the forthcoming -- potentially forthcoming revised guidance on leukocyte reduction will address, it has to first answer this key decision: Should FDA recommend a simple transition period of 12 months or briefer or should FDA support transition periods that are longer than 12 months which may allow further maturation of costs, clinical and scientific issues?

This is kind of like true/false questions on a test. You have two choices. You pick the longer sentencing, and you're usually right. I highlighted the longer one in red, which indeed reflects at least

one version, including my version, of how we should go about deciding on a time frame of implementation.

To expand on that a bit further, one proposal is the following: Recommend -- FDA may recommend that each blood center develop an implementation plan, not necessarily the whole implementation but develop a plan in six months. Six months is not too slow or not too fast. It's reasonable for a plan. But then the plan to be fully implemented for all whole blood and red cells at least, and potentially to also platelets -- depends on the consensus that we derive internally, based on your input, of course -- to implement all of this in three years.

Now that could be interpreted by many as being overly generous, overly lengthy, but many will argue that this is also quite an aggressive schedule. But the idea is to switch the default decision in the absence of definitive data either for or against ULR from not performing leukocyte reduction for all blood components to doing them in three years unless proven otherwise.

So rather than doing something and waiting for -- Rather than waiting for the data to appear before acting, you decide to act by a certain time

unless there is data against it. So this sort of represents a switch into thinking about the default mode of operation.

For those who think that the three years might be overly conservative, what we could do is hold an interim public discussion, perhaps in the form of a BPAC discussion, at the one-year juncture to determine if universal leukocyte reduction should be implemented sooner -- fully implemented sooner. So that represents one current version of FDA thinking about the implementation time frame.

Now all of this is to allow and actually encourage the maturation of scientific data regarding the current controversial indications of leukocyte reduction, either in the form of a consensus development or actually in the form of controlled clinical trials.

Many clinical endpoints, if you will, can be addressed, but the more important ones that most workers in the field are currently considering involve whether or not there truly is an immune suppression effect, whether or not truly leukocyte reduction can diminish the blood storage lesion, as well as strengthening the currently occurring data for reducing HLA alloimmunization incidence.

One consensus development conference is already planned and is scheduled, and I've seen the "Save the Date" notice of fliers -- I've noticed fliers already being distributed at the outside desk. This is being organized actually by Dr. Snyder and Dr. Blajchman from Yale and McMaster Universities and is entitled "The Clinical and Molecular Basis of Transfusion Induced Immunomodulation" to be held in Washington, D.C. in March 2000.

I'm sure there will be lots of interesting presentations at that consensus development conference, as well as any other future conferences that might be additionally held.

Additional studies are being planned or are currently underway, and these studies actually do include controlled clinical trials. I'm aware that the Massachusetts General Hospital either has begun or will shortly begin a controlled trial on leukocyte reduction.

At this juncture I'd like to just point out one study that represents recent data on microchimerism after blood transfusion that is quite interesting and appears relevant to today's discussion. I don't want to violate the ground rule that I referred to this morning, but I believe it is worth pointing out, at

least in one slide.

Please excuse the amount of words on this slide, but I didn't want to take up too much number of slides on scientific data. But I think by now some of you might be hungry for actual scientific data. So it's probably reasonable to present this slide.

There was a paper published in Blood in May of this year, and the lead author is Dr. Lee, unfortunately not this Dr. Lee but Dr. Lee, nonetheless, with the senior author of Dr. Mike Bush from formerly known as Irwin Memorial Blood Center.

The title of the paper reads as "Survival of Donor Leukocyte Subpopulations in Immunocompetent Transfusion Recipients: Frequent Long Term Microchimerism in Severe Trauma Patients."

What the study looked at -- They looked at two groups of patients, one set of eight elective surgery patients and a second set of ten trauma patients. The difference between the two groups is the number of blood units that they received.

Now all of the blood units that these subjects received -- patients received were not leukoreduced and not irradiated. The elective surgery patients received either one or two units, a mean of 1.5 units, and the trauma group patients received at

least four and up to 18 units, typically ten units per patient.

What Dr. Lee and the rest of the investigators did is to analyze the persistence of donor derived blood cells by a technique called quantitative allele specific PCR, polymerase chain reaction, and they actually targeted male to female transfusions as a way of tracking donor cells. Not that male to female transfusion was an important aspect, but it allowed the tracking of the donor cells in a recipient for long periods of time.

When they looked at it using this technique, they were able to show that in the elective surgery patients these cells transiently proliferated from days three to five in most patients, but all cells were completely cleared below the threshold of detection by this technique within two weeks in all patients. However, in the group that was heavily transfused, in the trauma patients, the ones that typically received ten units, the cell survival was documented up to 1.5 years after the transfusion, and it included multilineage cells, CD4 and CD8 as T cell markers, CD15 as the myeloid marker, and CD19 as the B cell marker.

They were able to show by additional HLA

typing studies and one-way mixed lymphocyte reaction studies that these were actually of single donor source, and they represented donor cell engraftment without clinical transfusion associated graft versus host disease.

So that's very intriguing. Obviously, it's a very interesting and important paper, but it should be followed up with additional studies, potentially leading up to controlled clinical trials, to determine what meaning this has clinically for the typical transfusion recipient.

So what does it mean? What could it mean for the transfusion induced immunomodulation? It appears that this multi-transfused patients, there is evidence of tolerance to donor cells, evidence of clinical transfusion associated graft versus host disease. Professions used that term, because there weren't anything clinically evident that showed that there were any graft versus host disease going on.

Potentially, that represents some degree of immunosuppression. Perhaps this is one mechanism of immunosuppression that's being discussed among recipients of blood.

It appears engraftment is more likely with more transfusions. It appears that increased post-

operative infections and tumor recurrence that we have seen in some studies could potentially be related to this phenomenon.

Does this mean that universal leukocyte reduction should be considered in conjunction with gamma irradiation, since irradiation is the method of choice for eliminating transfusion associated graft versus host disease?

Does this mean that we should revisit the irradiation induced storage lesion, along with universal leukocyte reduction, because the current data on the fact that irradiation shortens blood unit shelf life is really based on limited data, and also it does not take into account the fact that leukocytes might mediate whatever effect on storage lesion irradiation had?

So I think there is additional considerations that must be -- That, fortunately, will be forthcoming in the next several years.

Okay. I hope I haven't violated a ground rule, but that's an interesting tidbit to consider. The way I justified it in the framework of this talk is that I think those are interesting considerations that support a longer phase-in or transition period to allow data maturation with potentially the interim discussion

at one year to act more aggressively, if indicated.

Moving on to the next question: Should FDA recommend specific implementation criteria applicable to all blood establishments or should FDA provide only the framework within which blood establishments adopt an implementation plan specific to each center?

Once again, if you are a good test taker, you highlight the longer sentence, and that's my position here, that we should provide some framework but allow each blood center who know their operation best to develop each specific implementation plan. This is consistent with the comments that have been made previously.

So if we were to decide on a time frame of three years to full implementation, in the absence of definitive data either for or against ULR as the default decision, then it would be up to each blood center to develop its own specific implementation plan, subject to FDA verification that they have a plan, perhaps at an inspection and perhaps in FDA comments if the plan is unreasonable.

The plan will most likely address the milestones in terms of time, as to where they will be with passing of time during the transition period -- for instance, X percent of all blood units manufactured

by Y period in time, and whether or not the blood center strategically picks one blood type over the other before proceeding with universal leukocyte reduction, and whether or not the leukocyte reduced blood components should preferentially be triaged to certain patients for certain patient indications.

Those are physician decisions that are even beyond the control of the blood center, but actually resides at the level of the hospitals and the treating physicians.

The issues regarding additional staff that might be necessary, additional training that might be necessary, additional equipment, laboratory space and inventory control -- these are all complex operational issues that each blood center is best equipped to decide for themselves.

Then I will move on to the third question, which reads: Should the current FDA guidance on leukocyte reduction be retained for use during the transition period or should the definition on quality control of leukocyte reduction be updated from the current FDA recommendations for implementation during the transition period?

Now here, if you apply your test taking skills, you would be wrong, because I actually favor

the shorter sentence, that we simply retain it, just to analyze -- just to separate the variables in time. I don't think we want to attempt too much all at once, but do it one step at a time.

This is not to say that our current recommendation is perfect. It certainly could be improved, as I'll illustrate as follows: The current recommendations say that you should sample a minimum of one percent or four units per month, whichever is greater, and the sample may come from the units that have been manufactured in the previous 30 days, and with the requirements that the level of residual leukocytes remain at five times 10^6 cells per unit or below, with a product recovery of at least 85 percent of the red blood cells.

If a blood center applies these QC criteria and receives acceptable results, then does it assure a robust leukocyte reduction process? I mean, how robust is it? What do we know about the possibility of unacceptable products slipping through?

If we pick a scenario where a blood center manufactures and leukocyte reduces 400 red cells per month, suppose an error in filter priming procedures used by a new staff member results in achieving acceptable final product standards in only 80 percent

of the leukocyte reduced units, and that's probably an unacceptable situation where 20 percent of the units that you believe to be leukocyte reduced is actually not and, since you're not testing every one, there's no way to know that.

Per FDA recommendations, the blood center performs quality control testing on four units, and the units are all satisfactory. Well, what does that tell you about the fact that everything is okay?

I applied this simple formula with the guidance of statisticians within the agency who cautioned that this is applicable only with large N or with large number of products produced, but not applicable when the numbers are small. Be that as it may, I think that still serves to illustrate a point.

The probability of obtaining a good unit, given the flaw in process procedures, is 80 percent. Then the chances of obtaining a good unit four times in a row is 41 percent, and that the chance of obtaining at least one bad unit by applying this QC criteria is one minus that or 59 percent.

That's not very good in terms of sensitivity, in terms of your ability to pick up the significant deviation that might be creeping up and might persist for months unless you do other QC

testing.

You could generate a table full of numbers based on similar calculations for other sets of N or total number of units and other criteria, other thresholds that you feel is acceptable. For instance, across the top, 50, 60, 70, on through 99.9 represents the number of good units that your current procedures are producing in terms of leukocyte reduction, and it remains to be debated as to exactly what is acceptable.

Obviously, if your procedure is generating 80 percent with 20 percent units not meeting criteria, then that requires correction. But perhaps 90 or 95, perhaps 99 -- where is the threshold of acceptance? Ninety-five appears a reasonable number at this point.

Along the lefthand column is the total number of units and the total number of QC units that are required per current guideline. When you are making only 100 units, you would still test four. At 400 you would test four as a one percent. Then as one percent on up forward -- upwards of 10, 60 and 100 units.

If you apply similar thinking, I think for you to have 95 percent level of confidence, that at least 95 percent of the products that you manufactured meets the criteria that you think you're manufacturing.

You need to be testing 60 units. That's independent of the total number of units that you are manufacturing.

In other words, if you make 6 million units, you still only need to test 60, but again, as pointed out by my statistical consultant, this analysis falls apart as the number of units that you test approaches -- number of units that you manufacture approaches the number of units that you actually test.

So, in fact, for most small blood centers the QC testing requirement to achieve 95 percent confidence level should be well below 60, but it certainly is larger than four, as is specified currently.

Just to point that out but not to actually argue for changing the recommendation, but I think we should probably retain the recommendation but keep this in mind and work toward perhaps making the QC process more robust.

So as a summary then, in terms of QC there seems to be some room for improvement, but it appears that there need to be no maximum -- there need to be no need for testing beyond the maximum of 60 units per month. The number 60 is not engraved in stone, obviously. This is just a number that I have derived

by briefly thinking about the process.

The current method of sampling once a month means that, if some error creeps into your process, you won't know it for a whole month. That doesn't seem desirable. Seems like it should be more frequent than monthly sampling.

In terms of the actual residual leukocytes, five times 10^6 cells per unit in the product recovery thresholds still seem reasonable for the moment.

So I think what we would like to probably move toward in the future in terms of QC recommendations is to perform in such a way to have 95 percent confidence that 95 percent of your process units meet leukoreduction standards. That's a criteria that's not currently specified and, therefore, it is not necessarily being applied at all blood centers.

Okay. So the summary of the potential revision to FDA guidance on ULR for whole blood and red blood cells: I think the planning process should probably occur by six months with potential interim discussion at one year, with potentially full implementation in three years, and each center to design its own implementation plan, and retain the current recommendations on process control for now, for sake of separating out complex variables.

These general guidelines may be also applied to ULR for platelets, but platelets will be discussed in much more detail by Betsy Poindexter immediately following this presentation.

These recommendations -- The purpose of these recommendations is to allow an encourage maturation of leukocyte reduction as a clinical science, and also to absorb and cushion reimbursement concerns, and to potentially avoid -- avoid any potential adverse impact on blood availability, including health care delivery.

So, basically, leukocyte reduction clearly by now is no longer a method to manufacture a choice product. It's coming as blood GMP, but the conservative implementation of ULR as blood GMP will probably be the best route, in the absence of definitive data for or against universal leukocyte reduction as the default decision.

So this is rather general, and may also be impractical to platelets, but I think I'll reserve my comments to potential revisions of guidance for whole blood and red blood cells to this for now.

That concludes my talk.

(Applause.)

DR. HOLNESS: Thanks, Jong. The next

speaker is Betsy Poindexter from the Division of Hematology. Here at CBER Betsy is considered the queen bee of platelets. Betsy will speak on revised guidance on platelets and platelets pheresis.

MS. POINDEXTER: It's still morning. Good morning, everyone. I'd like to thank you for giving me the opportunity to make this presentation.

The title of my presentation is the expectations of the FDA with regard to whether we need to revise guidance for platelets and platelets pheresis. I will attempt to cover -- and for those of you who may not be as aware of the various types of leukoreduction in a very brief overview describe those, describe the current regulatory process for submitting platelet and platelet pheresis samples to the Center, and the regulatory process for applications that might be involved, the labeling issues that might be involved with the leukoreduced products that are currently licensable and are licensed every day by our Center, the distribution of products that may not meet the current standards for platelets pheresis, particularly because they are single donor platelets meant for a single transfusion dose to a single patient, unlike whole blood derived platelet concentrates where a pool of products is used and the patient might receive four

to six units, so the potential as to whether we need to revise the guidance documents that are currently in place, if we do go in the direction of leukoreduction, what its implication will not currently include, to look at some areas that we need to maybe stop and be aware of and to investigate and to listen to what the manufacturers are telling us and what the other blood centers might be telling each other, as well as we at CBER, and then I will discuss my conclusions.

Currently, there are many different types of leukoreduction. There are the in-line integral filters that are currently attached to many of the whole blood collection sets, many of which involve filtering either the whole blood unit and producing a leukocyte reduced whole blood unit that can be then processed into red blood cells or platelets, and some of the units also contain an in-line or integral platelet filter so that you spin your whole blood. You then filter your platelet rich plasma into a collection container, add your additive solution, and produce your red cells, spin your platelet product, produce a leukoreduced platelet concentrate and an FFP product.

There are also continuous flow in-line filters for some of the apheresis devices. There are filters now that are manufactured that are freestanding

with a filter unit and a storage bag for the production of leukoreduced red cell products, and there are now a generation of automated apheresis devices that allow one to collect the platelet pheresis product or multiple platelet pheresis products without the use of a filtration device.

Our goal, if we go toward universal leukoreduction, is to have these processes done in a blood center or a laboratory rather than at the bedside or at a transfusion service on a product for which we have little or no control over the processing of the filtered product.

I have some cartoons here to describe those filter units that I described. The first is the one that people most frequently see currently, is an in-line filter. That second red blood cell bag is supposed to be attached. The second, the post-processing filter, is one that can be used on a product within the eight-hour room temperature hold or at three to five days post-production.

The diagram on the left describes what is currently in the Heamonetics MCS-Plus device. The platelets are collected in that process mode, and each of those batches of platelet pheresis product are then delivered through a filter and delivered into a final

storage container.

The process on the right is currently available through the Cobe and Baxter systems where the product is natively leukoreduced just by centrifugation process and yields a leukoreduced platelet pheresis product.

The filtration of platelets and platelets pheresis involves a variable number of filters. Each of the manufacturers has provided very specific information about the use of their products, and these instructions for use should be specifically used for each of those products in the blood center.

This is one of the areas that at least currently we cannot just take one set of processing procedures and say one sizes fits all.

In addition to specifically following each of the manufacturers' instructions, studies have shown that you should not use any sort of mechanical force, whether it's manually squeezing the product to be filtered or applying a blood pressure cuff around the unit to increase the flow through the filter. It has been shown that not only does it cause hemolysis in the end unit, but it does not leukoreduce the product.

If the QC results indicate that the product is not leukoreduced, then you should not put a

leukoreduced labeling on your product, and it should definitely not be leukoreduced a second time. We have not received any data to support secondary filtration through any of the filters that are available.

Again, I want to stress following the directions for use for each of the filters that are involved and each manufacturer's variations on filters. They may not be identical.

For platelet products, in particular, produced form whole blood and from platelet pheresis procedures that may go on to be filtered at the end of the process, do allow for the rest period that's recommended by the manufacturers.

Through many of the centrifugation processes, both from the whole blood products and the apheresis devices, the platelets that are initially in that primary storage container or collection container are slightly jazzed up and are activated to a slight extent, and they need a tim period, generally an hour to two hours, to -- I call them happy campers -- to be happy campers, and then be allowed to go through the filtration process.

Products that have been allowed to go through this process then can be labeled as leukoreduced products, assuming that your process is in

control and that those units that you are testing have met the current guidelines for labeling leukoreduced products.

For licensing procedures for licensed -- for centers who currently have a license for whole blood derived platelets pheresis, we have not required any additional product submission.

What we have asked is that they validate the process within their blood center, that they validate their QC method to make sure that their QC method allows them to count to the levels that are necessary for them to be able to label those products appropriately, to perform the monthly QC that is required by the regs and by the current guidance documents, to investigate all procedures.

Don't just write it off and say, well, you know, sometimes filters don't filter or sometimes filters leak. Try to figure out, either through your own investigation or discussions with the manufacturers exactly what might have gone wrong.

With the apheresis devices, we'll come to that later. There are other methods for going into this.

Make the SOPs that you have available for both your process, your validation and your labeling

available for our inspectors upon time of review.

For unlicensed products that are kept within the state, the same criteria apply except that we, the Center, will not have seen any of those SOPs perhaps for smaller sites that maintain all of their products within their state.

The inspectors would be fully aware of those, and it is not infrequent for us to field phone calls from inspectors on site, wondering whether a particular method, counting methods, have been validated in enough people's hands and written in scientific literature for us to make those determinations as to whether those counts are really accurate or not.

For licensed platelet pheresis procedures for leukoreduced products, both for filtered products and for apheresis in process, leukoreduced products, we have required and requested licensed applications for each particular variation on a theme. In addition to the initial four criteria, we do ask that the centers currently submit either the license application forms and rapidly on the heels of that the biologic license application, including an SOP for CBER's review.

We do review those SOPs concurrently with your product license applications. In addition, we ask

for at least two months' worth of in-house quality control on your leukoreduced products or any other apheresis products that you might be producing on that particular instrument or filtration.

We do still require samples to be sent to the Center for our evaluation and comparison to the results that the blood centers might have gotten.

It is not infrequent that we have concerns about particularly the volumes that are being put on the platelet pheresis products. We have had volume determinations that have been off by 40 and 80 grams.

Now that makes a considerable difference in the total yield of the platelet concentrate or the platelet pheresis products, but where it is particularly of concern is that the volume then that is used to store the final product may not adequately -- the plasma volume that's stored may not adequately reflect what is able to go into a particular storage container.

Forty and 80 grams usually represents one bag weight or two bag weights and the tearing of the balance, and we made a presentation at AABB this year, but this is a very frequent error.

For unlicensed products that -- unlicensed pheresis products that are kept within the state, the

same validation process, QC method, monthly quality control, and investigation of all failures of the product to meet the leukoreduced criteria should be met. In addition, the SOPs that are being used by the blood centers should be available for review by inspectors at the time of review.

We frequently encounter calls from blood centers saying, well, what is the proper product code for platelets that are leukoreduced or for platelet pheresis products that are leukoreduced. So I have provided those product codes. You can take them back to your center. We do have those on guidance documents that are available through Ken Zieman in the Division of Blood Applications.

These are for the whole blood collected products, and these are for the pheresis products. As you may be aware, there are capabilities of producing single, double and, in some cases, triple platelet pheresis products on the apheresis devices, each of which must meet the 3.0 times 10^{11} platelets and the leukoreduction standard, if that standard is being used for your products.

For less than standard content products, those products that have less than three times 10^{11} platelets, we do not allow those products to bear the

license number. Our policy has been that those products can be used within your state with the other than standard content label and with a tie tag or a sticker on the bag that indicates what the final concentration of the unit is. As you can tell from the asterisk, these should not bear your license number.

We have allowed variations of plus or minus ten percent. So three times 10^{11} or 2.7 times 10^{11} to bear the other than standard content. Concentrations which are less than that may not adequately store in the storage containers that are currently available, and will require further investigation.

Disposition of products -- and I've covered a little bit of this already: Platelets containing less than 5.5 times 10^{10} platelets, if you know that in advance, you should put an other than standard content label on that bag.

Obviously, we don't count every single whole blood platelet that we produce, but if it's a filtered product and you do have a pre-filtration count and a post-filtration count and you do know that that's less than 5.5 times 10^{10}, you have the option of putting that label on it.

For platelet pheresis products containing less than three times 10^{11}, they should be labeled with

the less than standard content label. The platelet content should be put on the label. It should be used within the state, and I pretty much covered this in the previous discussion.

Jong Lee discussed the current guidance documents and perhaps our need for modifying the documents that are there, based on the information that we might derive from today's discussion. We currently have at least two documents out there, one being the 1988 guidance document for the collection of platelets pheresis.

It is something that we are considering updating, particularly to include the multiple product collections as well as the leukoreduced product collections, and then we have the recommendations and licensing requirements for leukoreduced blood products from 1996.

Based on our discussion here today, and possible disagreement with Jong, maybe we will want to modify that to have more information about process control and statistical analyses of the data that we do collect at the blood centers.

In the future, we do plan on updating the platelet pheresis guideline, and perhaps we should consider modifying the draft apheresis red cell

guidance document to include leukoreduced red cell products. Currently, that is not addressed in that document.

Should we change the current definition of leukoreduction? The current international standards are listed on the left in the orange print, and our current CBER standards are listed in blue -- recommendations, CBER recommendations.

The Council of Europe suggests that each of the products should contain one times 10^6 white blood cell units per transfusion dose, and there is a slight addendum there for the whole blood platelet products. They state that 90 percent of the units should meet that standard. We require 100.

They require a minimum of ten units per month tested for each product type, and they agree on the one count of the one percent of production.

Jong had discussed whether we should modify our monthly QC to perhaps be a more frequent event, so that we are able to track more carefully when our process might be falling out of control. I would like to suggest that we might consider a weekly QC process.

I know that there are some blood centers, particularly for the platelet pheresis products, that do weekly QC. They will take one double, one triple,

and one single product per week and test it for each of the machine variations that they might have on hand.

This could potentially reduce the number of massive recalls that might be involved if a process was found to be out of control at the end of the month and reflected whatever products you might have collected during that last 30 to 31 day period.

If the process is found to be out of control, we would like to suggest that any products that are still in-house be recounted to assure that they are truly leukoreduced. If they are not, then that labeling should be changed. If the products that have been released are recalled from the hospitals or transfusion services that may still have them on hand, they could be replaced with products that do meet the standard.

Obviously, products that have been out there for any length of time -- read after about three to five days -- any redoing of the leukoreduction -- the leukocyte counting by any of the methods currently available is probably only going to give you garbage information, because the cells will -- What few cells might still be there are going to start breaking up, and those products are probably a loss. But that's something is definitely up for discussion.

What implementing universal leukoreduction will not do at this time: Currently, it will not extend the dating of platelets and platelet pheresis products to seven days. We need to have additional studies performed to determine the effects of leukoreduction and, in some cases, super-leukoreduction on the platelet storage parameters.

At this time it won't eliminate the concerns regarding bacterial contamination. Although many studies have been done, and the data are inconclusive, the jury is still out regarding the ability of filters to remove a variety of bacteria or other microorganisms.

Currently, it will not allow blood centers to self-certify conformance to a CBER document on leukoreduction, because currently we don't have a document that could be referred to by the blood centers. But this is something that we could consider when a document such as this is available.

It will not currently eliminate the need for submission of products to the Center, particularly for the platelet pheresis products, and for new sites that are coming on line for whole blood derived platelet concentrates.

Although leukoreduction process in itself

might yield a product for which a leukoreduced product label could be borne, the processing itself sometimes doesn't yield quite the product that the blood centers might hope for, primarily due to their not adequately following the instruction manuals of the instrument manufacturers.

Okay. So this is sort of my stop, look, and listen. Stop: The purpose of this universal leukoreduction proposal and potentially implementation is to eliminate transfusion service and bedside filtration for which we have no process control.

I'd like everyone to consider investigating your process. If your processes are out of control, to seek help, if you don't have help in-house, for finding where your could improve your process, improve your counting method, your sampling method, the numbers of samples that you might be testing; to investigate your long filtration times.

At the AABB this year, there were a couple of presentations by physicians who had remarked that long filtration times frequently occur in donors who have sickle trait.

If sickle trait is an item that might cause filters to not filter in a proper amount of time and might not actually leukoreduce the product at the end

of the filtration process, we may have a concern, particularly during a time when we're trying to enlist minority populations to donate both for HLA typing for bone marrow transplantation and for transfusion products that are particularly matched for their ethnic population.

Failures to produce leukocyte reduced products should be investigated, not only through your past performance but also with manufacturers of the filter devices. Many of these manufacturers are more than willing to send people on site and to watch your process and to assist you in making this process work for everyone.

Too frequently, the blood centers will call in frustration, and we don't have the filters at CBER. We don't filter red blood cell and platelet pheresis or platelet products. At best, we read a lot and see an awful lot of applications from device manufacturers and from blood centers, but we don't have hands-on experience using these devices.

So that all that we can go with is sort of gut feelings about things. Frequently, we tell the blood centers to call the manufacturers of the devices and ask their technical staff for assistance.

Listen to the comments from your staff.

Don't just write them off as, well, she's always complaining that this filter doesn't work right. Maybe there's something to what that person is saying, and share that information with other blood centers within your region and other people within your processing staff.

If the eight o'clock shift doesn't know what the four o'clock shift found out last night, maybe that same problem is going to occur. Again, listen to the -- Ask the manufacturers questions, and listen to their responses and, most of all, read their package inserts and their directions for use.

My conclusions: Validate each process to be performed in the blood center. That may sound like a done deal, but there are centers that are out there trying to implement processes that have not been validated.

There are some instrument manufacturers who are claiming that they can count the leukoreduced products, and I can tell you that many of these manufacturers have not submitted 510(k) either to CBER or to CDRH for specific clearance for being able to count residual leukocyte loads in either red cells or platelet products.

Work with the manufacturers to improve the

quality of the process as well as the quality of the products. This benefits everyone, from the manufacturers of the devices to the blood centers and, most of all, to the patients who are going to be receiving these products.

Remember that any guidance that might be issued as a result of this workshop will be in draft format, and it will be ready and awaiting your comments, and we know that we will receive them.

Thank you very much.

(Applause.)

DR. HOLNESS: Thanks, Betsy.

Our next speaker will be Mary Gustafson. Mary is our Director at Division of Blood Applications, and she will speak on revised regulatory expectations.

CAPTAIN GUSTAFSON: Thank you, Dr. Holness, and just putting up my very low tech slides, my overheads.

I changed the title of my presentation somewhat from what was listed in the agenda. I think it says revised regulations, and I want to reflect the fact that we don't have revised regulations to present to you today nor have we started working on the section of the regulations that would include the leukoreduction.

You may have noticed that we have published some proposed regulations in the past few months, and I can attest to the fact that writing them and getting them through the clearance process is a very laborious, time consuming process. So we are sometime away from updating the actual regulations and the 640 additional standards that would include the leukoreduction.

What I will discuss -- I'll put my title up. What I will discuss with you this morning are some of my thoughts on regulatory expectations as they relate to universal leukoreduction.

First is the issue of licensure. Licenses are required for blood and blood components when those components are introduced or delivered for introduction into interstate commerce. This includes products that are modified by leukoreduction.

As Dr. Lee mentioned earlier, the approved indication that we have to date is for the decreasing febrile nonhemolytic transfusion reactions and, although some of the other indications that were discussed today are under study or under discussion, I do want to stress that we don't expect the implementation of universal leukoreduction to hinge on proving or disproving each and every possible clinical indication.

In fact, there's a part of me that's very, very happy that blood and blood components have been licensed for approximately 50 years, because I think it would be very difficult to get them licensed under today's scenario.

If an establishment is already licensed for nonleukoreduced blood components, the addition of leukoreduction is a change that is to be reported as a prior approval supplement to your license that requires currently review and approval prior to distribution of the leukoreduced product.

What does this mean in terms of regulatory burden for us in reviewing applications, and for you, the industry, in submitting applications, waiting for approval and implementing the change? My answer to that is I really don't know.

Unlike the initial licensing of irradiated blood components several years ago in which we had a sudden influx of license applications that took us a couple of years to kind of crawl out from under the heap, the leukoreduced blood components have been licensed for many years.

A search of our database reveals that many licensed establishments are already licensed for leukoreduced red blood cells and a somewhat smaller

number licensed for leukoreduced platelets. What is not clear by reviewing our database is how many of you will need to add more processing facilities to accommodate universal leukoreduction or update your license applications to reflect more up-to-date technologies.

We don't have a handle on all of the technology changes that may be in design or development by the device manufacturers. In addition, it is not known how many new applicants will pursue licensing.

My initial impression is that the implementation of universal leukoreduction will not result in a huge influx of applications, since so many establishments are already licensed. However, I tend to be a Pollyanna, and also this could change with the technological changes that come along with implementing a new process and the advances within that process.

The recommendation from the Blood Products Advisory Committee was made slightly over one year ago, and many have already ramped up and submitted new or updated license applications. We expect the timeline for implementation to be gradual enough to accommodate spacing of applications.

I do want to stress again that any implementation plan and proposed timeline is a straw

person for discussion today only. We thought that putting together a straw person plan and timeline would stimulate more discussion than trying to deal with just an abstract concept, without giving you any idea of what may be anticipated.

If I could have the next slide. We do have some plans, though, to offer some regulatory relief, and these are plans under our existing action plans.

Approximately two years ago, the agency undertook a systematic approach to implementing changes in our blood program. The changes needed were precipitated by oversight investigations, including Congress, the General Accounting Office, the Department's Inspector General, the Institute of Medicine, and others on the outside; and amazingly, we were also able to add some of our own initiatives that we wanted to accomplish.

The compilation of actions is termed the Blood Action Plan, which is what is showing here, and we also have a Device Action Plan. The plans clearly address tasks to be performed and prioritizes work.

As you may be aware, we are a big bureaucracy. One of the problems in the past in reaching the end zone in any task was individual components priorities. You would work really hard on

something that was very important to you, only to find that the next agency component that was to move the task had their priorities which didn't include your priority.

The Blood Action Plan provides a framework for agency and, in some cases, Department prioritization of every initiative. The Blood Action Plan has six areas of emphasis with assigned teams that is directed by an umbrella core team.

I direct your attention to the third bullet entitled "Reinvention of blood regulation," which I noticed this morning had a typo. It's the one on there that I wanted to talk about, and it's the one with the typo.

The team has as one of its tasks the initiation of a pilot program for licensing by self-certification of compliance to a monograph standard. The self-certification licensing scheme is intended to supplement and, in some cases, replace our current licensing mechanism of reviewing an extensive license application submitted by the applicant prior to issuing a biologics license approval.

The monograph standard is an FDA guidance document developed under our standard operating procedures for developing guidances under good guidance

practices. One such guidance for irradiated blood components published for comment last year, and should be publishing as a final guidance very, very soon so that we can begin the pilot in that area.

Another guidance for red blood cell immunization of source plasma donors is nearing completion internally, to be ready to publish as a draft for comment early next year.

We have envisioned adding a third pilot to the program to include licensing of leukoreduced components, at least red blood cells. We have begun early, early efforts in writing a document, and your input today on whether this would be a valuable exercise and what elements of the guidance would be helpful.

I think, in Dr. Lee's -- maybe it's question number 5, it mentions about the guidance document and the self-certification pilot. I do want to modify that a bit when you see it again. I think the issue would be whether the content of the 1996 document should remain the same.

Our Associate Director for Policy at the Center level is not here today, which is good, because we pretty well have a mandate that we will put all of these memos that we have into good guidance practices.

So I think it mentions using the memo as it is, and we will need to revise and put that into at least the format for good guidance practices, but the true issue is whether we need to make changes in the content of that document in order to have a self-certification pilot initiated.

Also, in addition to the licensing for the individual manufacturers of the leukoreduced products, I did want to discuss a bit about device manufacturer issues. I don't have an overhead, but under the Device Action Plan the FDA is committed to meet the statutory timelines for review of device applications.

These are 90 days for a 510(k) and 180 days for a premarket approval application. In order to maximize our review process, I cannot emphasizes enough the importance of early and frequent contact with FDA during product design, actually inception design, development and the testing phase, in order to ensure that the application that you submit to the FDA will be reviewable within the 90 days and will be reviewable within one review cycle.

Okay. In addition to action plan issues and licensure, there are some other regulatory issues that are perhaps more in the future, but I will touch on those a bit.

One issue, and it was one that Dr. Snyder mentioned, was what will become of the nonleukoreduced blood components? I believe Dr. Snyder mentioned that they should go the way of fresh whole blood. Another term for that would be basically will they become obsolete or should they be allowed to coexist with leukoreduced components, as is the current situation?

FDA regulations include a section entitled 21 Code of Federal Regulations 601.5 that outlines the grounds for revoking a biologics license. One of the grounds is that the licensed product is not safe and effective for all of its intended uses or is misbranded with respect to any such use.

Does the leukoreduced product offer such clinical advantages that the nonleukoreduced product should be rendered as no longer being safe and effective and, therefore, should the licenses for the nonleukocyte reduced components be revoked?

Is this my lucky day or what? Another initiative under the Blood Action Plan, as I mentioned before, is the systematic review and updating of blood regulations. I don't think people like regulations or the regulatory process. Did you all pay him to do this?

We have our additional standards for blood

components in Part 640 of Title 21 of the Code of Federal Regulations. As we update those standards and add leukoreduction, should we specifically add leukoreduced products as new components or should the processing steps for the current components be updated to include mandatory leukoreduction?

In essence, rather than having leukoreduction as a manufacturing option, should leukoreduction become the standard for all blood components? This, by the way, is what's happening in Canada, because they have requested labels for plasma and cryoprecipitate, and basically everything as being leukoreduced.

Another future consideration is the issue of labels and labeling. Currently, the container of each leukoreduced component identifies the component as leukoreduced. As we move to universal leukoreduction, will the addition of the verbiage to each container be unnecessary?

There's limited room on a blood collection container. The real estate is -- As we design for ISBT 128, there's all kinds of discussions on what has to be in there and what doesn't have to be in there. So if everything is going to be leukoreduced, does each container have to say so or should we remove the term

from the container label and have the processing steps of leukoreduction be added as statements to the circular of information?

These are the types of regulatory questions we are considering. You may think of more, and I invite you to mention those to us today. We invite your comments and ideas as we develop our regulatory strategies for universal leukoreduction.

Thank you.

DR. HOLNESS: Thanks, Mary, for persevering through those trying conditions.

The final speaker for this session will be Larry Fenner. He's with the Division of Case Management, the Office of Compliance and Biologics Quality at CBER. His topic will be compliance and blood quality during the transition period.

MR. FENNER: Bear with me while I load my program. We can maybe change some screens during that time. This isn't my laptop, and I don't know what I'm doing. I'm okay.

Okay. My topic today is compliance and blood quality during the transition period. I'm going to talk about compliance as it relates to the regulations and guidance documents, the manufacturing processes, enforcement, and also an opportunity to

appeal.

My first topic is the regulations and the guidance documents. I'll assume that everybody is familiar with the Code of Federal Regulations, but just in case if you aren't, there are some blank pieces of paper in your folders today, and FDA would appreciate it if you would put your name and the name of your institution and the address on them, and pass them to the middle aisles, and we'll gather them and send somebody out from the local district office who will acquaint you with the Code of Federal Regulations.

Since the CFR is published subject to the notice and comment rulemaking process, the rules that are in CFR are binding requirements. On the other hand, we have the guidance documents.

The purpose of guidance documents is to provide assistance to regulated industry by clarifying statutory and regulatory requirements and compliance expectations or also to provide specific review and enforcement approaches to ensure effective, fair and consistent implementation by FDA.

They do this by explaining how industry can comply with the requirements. Some guidance documents provide information about what the agency considers to be important characteristics of preclinical and

clinical testing procedures or manufacturing processes, as in the case of the leukocyte reduced products, and scientific protocols.

Others explain FDA's view on how to comply with the relevant statutes and regulations and how to avoid enforcement actions.

The term guidance documents includes documents that are prepared by either FDA, applicants or sponsors, and also the public that relate to processing, content and evaluation or approval of submissions. They can relate to the design, production, manufacturing and testing of regulated products.

They describe the agency's policy and regulatory approach to an issue, and they establish inspection and enforcement policies and procedures.

Guidance documents do not normally include documents that relate to internal FDA procedures, agency reports, general information documents provided to consumers, speeches, journal articles and editorials, media interviews, press materials, warning letters or other communications that are directed to an individual person or to a firm.

The good guidance practices document established FDA's general policies and procedures for

developing and issuing guidance documents. It was published in the Federal Register dated February 27, 1997, and the purpose of that document was to ensure that guidance documents are developed with public participation such as this meeting today, they're readily available to the public when they are published, and that they are not applied as binding requirements.

All guidance documents include a statement of nonbinding effect that says that the guidance document represents the agency's current thinking on whatever, today leukocyte reduction. It doesn't create or confer any rights on or for or on any person and does not operate to bind FDA or the public, and we always give the opportunity to use an alternative approach, as long as that approach is as good as or better than the one that we recommend.

My next topic is good manufacturing practices. The information that I'm going to give you today was taken from the preamble to the GMP regulations in 1978, and FDA in those preamble -- it said that FDA determines what is considered to be cGMP through experience, through inspectional and compliance activities, through review of new applications and other submissions, and also through the consideration

of comments from interested persons in response to proposals that we send out for amending the cGMP requirements.

For a practice to be considered to be cGMP, the practice must be current in the industry. Congress did not require that a majority or any other percentage of manufacturers already follow the proposed mandated practices, as long as it was current, good manufacturing practice in the industry, meaning that it had been shown to be both feasible and valuable in assuring quality.

Now as far as enforcement, the investigators have a number of references that are available to them, and I'm going to talk about two of them today. The first one is the investigations operations manual, commonly known as the IOM.

The IOM is a primary source of the guidance regarding agency policy and procedures for field investigators and inspectors, and it directs the conduct of all field inspections.

It's available on the Internet at the address here. It's also in your handout. So you don't have to try to scribble it down, because there Internet addresses aren't the easiest thing to try to get real fast.

The IOM has very specific instructions concerning the use of guidance documents during inspections. What it says is you shouldn't reference the guidance document directly, but since guidance documents are normally based on GMP or other regulations, if the observation that the investigator makes during the inspection relates to the GMP, then they can put the failure to follow what we're telling you to do on a guidance document in a 483, just as long as it's based on the regulation.

So I will use as an example here the SOP regulations from the CFR. It's 21 CFR 606.100(b). That says, if you're doing something, you should have an SOP for it. So theoretically, if you're performing the procedure that's based on a guidance document, you should have an SOP. If you're not doing what you have in that SOP, you can be cited on a 483 for it.

The other reference guide that's available to FDA investigators is the compliance policy guides or the CPGs. They provide a convenient and organized system for statements of FDA compliance policy, including statements which can contain regulatory action guidance information.

It's also available on the Internet, and the address is in the handouts.

CPGs are usually written as a result of a request for an advisory opinion, a petition from outside the agency, or because of a perceived need for policy clarification by FDA personnel. It's not uncommon for a CPG to interpret regulations or guidance, and in some cases the CPGs also instruct investigators to use enforcement discretions.

For an example, if we have a regulation that's outdated because of new technology, a CPG may give instructions to an investigator that that particular regulation shouldn't be used as the basis for a 483 citation.

Finally, I was asked to talk about an opportunity to appeal. The process for the opportunity to appeal was outlined in the Federal Register of February 27, 1999, for the GPPs.

An appeal might be an appropriate action to take if a person believes that the GPPs weren't followed in issuing a guidance document or if a person believes that the guidance document has been used as a binding requirement, like if you were cited directly about a guidance document in a 483.

Very specific information is available in that Federal Register notice, and if you wish to go through this process, I suggest that you go to that to

get the specifics. But in general, what they tell you to do is your first -- You can go through -- up the chain of command.

In other words, if the investigator cites you, you should go to their supervisor, and then up through within the district or you can follow the specific center and office procedures that are available or also you can contact the Office of the Ombudsman, and all the information to contact the Office of the Ombudsman and very specific information concerning these other routes is also available in that Federal Register notice.

That's really all I have today. I have to go to another meeting this afternoon. So I won't be around for the question and answer period. So if anybody has any questions, I'll take them now. Good.

Thank you very much.

(Applause.)

DR. HOLNESS: Now it's time for lunch. I think Session III will start at one o'clock.

(Whereupon, the foregoing matter went off the record at 11:53 a.m.)

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

(1:03 p.m.)

MS. CIARALDI: Will everybody please start to take their seats, and we'll get on with our workshop.

I would like to welcome everyone to the second half of today's workshop. Thank you for coming back after lunch.

My name is Judy Ciaraldi, and I am a consumer safety officer in the Blood and Plasma Branch of the Division of Blood Applications. I will be moderating this third section.

In this session we will be hearing from representatives of the blood bank and blood center community. They will describe their experiences with implementing a universal leukoreduction and offer their proposals and recommendations for implementation.

Please hold your questions for each speaker until the panel discussion.

Besides introducing our esteemed speakers, part of my job is to make sure that the speakers stay on time. If they go over, I have been authorized to bring out the hook. In keeping with the holiday season, I'll be using this as my hook. I'm going to put it on the floor, as I sit right here; and if people

start getting close, I'm just going to place it on the table and kind of wiggle it a little bit, and people will know that they're getting close to their time.

Our first speaker will be representing the American Red Cross. Stephanie Norrell has a Bachelor's of Science in nursing from George Mason University. She joined the American Red Cross, Washington, D.C. region in 1986 as a QA coordinator for the nursing department.

IN 1996 Ms. Norrell was appointed Senior Director of Manufacturing Operations in the Manufacturing Department of Blood Services, and she is currently the Acting Vice President for Manufacturing.

I now present Ms. Norrell, who will talk about American Red Cross's experiences in implementing universal leukoreduction. Ms. Norrell.

MS. NORRELL: Good afternoon, and thank you for the introduction. Specifically, thank you to Dr. Lee for inviting us to speak today on the American Red Cross's experience in moving toward leukoreduction.

So when we actually made the decision that we were going to move toward leukoreduction, the very first thing we did was really look at what we had to work with when we started out. Basically, this is all we had to work with, a filter from each one of our

manufacturers and not much of the support or ancillary things that you need to implement leukoreduction.

So what I'm going to go through today, since we were asked to speak specifically on our experience, is really going back all the way to our internal decision making process, the planning process that we have been in and continue to work with, some of the system tracking issues that we're working with, issues, opportunities and challenges, and what our current -- saving the best for last, what our current conversion status is.

So taking us back through a little bit of history here, the BPAC recommendation, which was already discussed this morning, came out in September of 1998. At that time, there was no formal recommendation that followed, and in January of 1999 we internally performed a feasibility analysis to look at what our mission was going to be with leukoreduction.

We decided at that time that we were ready to move on, and thought it was the right thing to do. In April of '99 we initiated a task force to work the conversion issues.

The real instigators for movement in our organization were statements that were made by our COO at the time and by our Chief Medical Officer, Dr. Rich

Davey, and I'm just going to read those to you, because they were important mission statements, really, for us to get started.

So the COO at the time said that this is a change that will directly improve patient outcomes. The Red Cross would be taking a leadership role in transfusion therapy and reinforcing its commitment to patients, physicians and hospitals.

Right after he said that, Dr. Davey said, "As more studies on leukoreduction are conducted, and as benefits become clearer, it is apparent that prestorage leukoreduction is the right thing to do for our patients and for our health care system."

We then put together a cross-functional task force, because there were -- almost every department in a region and one of our centers is touched by this conversion. It's a major conversion for us anyway.

So the task force in our organization consisted of regional representation from at least five of our regions, subject matter experts. We had our QA/RA department in the task force, chief medical office, staff from the Holland lab, our manufacturing department both from engineering and planning and operations perspectives, and sales and marketing was a

joint partner with us during this initiative.

So this was the task force, and the task force is still actually in action.

The deliverables of the task force were fairly straightforward. We needed to look at our policies and procedures related to leukoreduction. We were at that point in time somewhere in the neighborhood of producing ten percent leukoreduced products, and we were looking at moving or converting the system to 100 percent. So, obviously, we needed to relook at our policies and procedures to make sure that they were in synch with that kind of a conversion plan.

We needed to look at our supplies and equipment, a filter mix allocation. What that really refers to is the fact that there are several different filter manufacturers, and we use filters from all of them. Not only do we use filters from the different manufacturers, but we also use different product codes from each one of them.

To further complicate it, our regions all at this point in time are using a mix of those filters. So there are some filter allocations and tracking that are important to us.

We needed to look at facilities and work flow issues, and produce a timeline for ramp-up. If we

made a statement that we were going to convert our system to 100 percent leukoreduced cellular products, we needed to at least have a target that we were aiming for. In fact, we do, and then, of course, keeping in mind the financial impact and so forth. One of the very early things that the task force did was to assess the current industry status and find out if there were things that industry had implemented in terms of equipment or work flow or whatever that we could benefit from in our conversion planning.

So we actually evaluated centers in the U.S., as well as in Europe, and actually learned a lot of valuable information, as you'll see later on in the presentation. We were also looking for some best practices as we went through that effort.

We also, very importantly, needed to assess our customer requirements. So we had made a decision, but were our customers ready to be there with us?

In fact, we did a market survey of about 300 hospitals. About 50 percent were Red Cross hospitals, and the other 50 percent were not. They represented small, medium and large hospitals, and what we found out from that survey is that 74 percent of them said they would be ready to convert by the end of 2000, if costs were not an issue.

We, of course, needed to obtain input from the staff that were going to be most affected by this change. That's the component lab staff, which we did, and identify any other issues that could be potential big hurdles for us to address.

We also identified some areas that we needed to research further. Different filter types: We knew of the ones that were immediately available, but we wanted to make sure that what we were looking at was the best possible solutions for our needs. So we actually looked at about 20 filters during this phase here, some of them available in the U.S. and some of them not.

We looked at the concept of a sterile dock shop. What that really refers to -- Because we have regions all over the country, what we were looking to potentially do is locate sterile dock shops where units would be collected and then sent to centralized locations where they would have the rest of the manufacturing process done at those locations.

Well, we assessed it, and at least at this particular point in time we're not ready to move there.

Sickle cell trait has already been spoken of today. There are issues when we try to leukoreduce

products from donors who have sickle cell trait. We are going to be performing a study, I think, in collaboration with the Army where we're going to be looking at three different filters and looking for which filter works the best, actually, with that type of donor, and looking for other things that we can do to enhance that part of the process.

Timing studies: With each one of these filters, they are unique, and so we had to find out which filters we could work with in efficient manners. So with each one of the filters that we use today, we have performed timing studies.

What we found as a result of these reviews is that we really did need to make some process enhancements, because we had been leukoreducing so little in our organization that our processes really had not been developed to be efficient when you're doing large scale leukoreduction.

So we began in earnest and looking to provide some burden relief in the procedures as they stood. We evaluated work flow and space issues, the different filter limitations. As you know, there are different head heights required when you're doing leukoreduction with the different filter manufacturers.

There are different timing with the actual

filtration process. So we really needed to understand the filtration limitations.

Equipment limitations, we ran into as we did our assessment in the beginning. The component lab staff were having serious problems with repetitive motion injuries with the stripping of the segments and so forth. So we had to assess ways to deal with those types of issues, looking at different ways to deal with the staff going in and out of refrigeration and so forth.

We also had to really concentrate on the QC issues, and that's been talked a lot about this morning. In our organization we are doing QC primarily with the manual method, and so you can imagine the impact of going from ten percent to 100 percent using a manual method of QC.

So we really had to begin at the beginning, and that was literally visiting each one of our regions and evaluating their facilities and the facility design, and how they would implement leukoreduction.

Leukoreduction takes more space. It just does, and so some of our regions have actually been constrained because of space requirements, the inability to add refrigeration space, and so forth. We had to look at them in terms of -- We began to look

at them in terms of small, medium and large, what type of filtration they were doing, and any other issues that were relevant to their local area.

Based on the information that we had heard from the component lab staff and during our walk-throughs during these work flow assessments, it became very clear that the equipment that has been available to the industry for leukoreduction really isn't appropriate when you go to 100 percent leukoreduction.

So we really began to think about having to -- Well, we went out and looked for equipment, even asked some of the filter manufacturers if they would like to come up with some equipment for us, and in the end some of the equipment we are developing ourselves internally.

Then again the operational procedure enhancements, which we've talked about.

So with the help of computers, we've actually done some modeling. For each type of filter -- this is, for example, an in-line whole blood filter. For each type of filter that we use, sterile dock, etcetera, and for each product that we're making, and for each size of center, small, medium or large, we have a template like this which shows the appropriate work flow or a template for a work flow.

So this is something that will be provided to all of the regions in their planning process as they go forward. It actually starts from when the unit comes in, processing. The red arrows cover the red cells process, and the yellow is actually plasma, the path for plasma during this.

It takes it all the way to the point where you've completed the leukoreduction process. So this is now complete for all of the different variables that I've talked about.

When you begin to think about carts, carts -- you know, it just seems like it should be such a simple thing, but in fact the carts we were using -- some of the regions were still using IV poles and so forth. That was okay when we were doing a very limited number of leukoreduced units, but when you go to full force, 100 percent, there is a lot of movement of these units back and forth from the refrigerator.

So we began to look t a model of a cart where -- We also found that, for some strange, unknown reason, a lot of people who work in the component lab were short. So with all the various head heights of these filters requirements, it can be very high, and it's hard for these staff to reach and so forth.

So we actually are in the process of

developing carts with variable head height adjustments and can actually come down low enough for short people like myself. So they actually also hold more units than any of the carts that we have seen available on the market today. So this is a very early prototype, and we're hoping to be able to implement it fairly soon.

Another issue that came up with the staff as we were doing our early assessments was -- you know, they have to spend a lot of time in very cold environments, going back and forth into the refrigerator, sometimes doing some of the actual procedural steps in the refrigerator, and they weren't really happy about that.

So one of the things that we identified on our European assessment was this reach-in refrigerator concept. There are two models that we're looking at, one that's actually mobile, on wheels, and one that's actually just stays in place once you install it.

What that allows you to do is actually batch your work and take advantage of not having to move the product back and forth, in and out of the refrigerator. It is looking in very preliminary pilot data for us as a very efficient new piece of equipment for us. So we are very excited about this.

The templates that I talked about, those are being -- will be used by every region to plan their floor space. Some of the regions actually are going to need to have build-outs, because they're just space constrained.

There are floor plans in there, etcetera. There is also an additional binder that's going out which has information, for example, about change control, that they need to be working on in parallel during the actual conversion process, because there is a lot surrounding this.

There's validation if you're implementing a new filter. There is all the training involved, etcetera, etcetera. So we're providing some templates for change control during the conversion process.

It also has some templates for marketing information, and the number of FTEs or staff required, depending on what filter methodology a region is intending to use and so forth.

The system tracking is very important to us, because we have a large system, and the real reason that I'm addressing it here today is because it became a critical path for us on our conversion process to track how many of these filters we were going to -- we were forecasting to use, because the filter

manufacturers have had some difficulty in keeping up with the conversion rate in this country.

So we have literally been almost on a weekly basis tracking filters that are going to be needed across the country for the following week, and working hand in hand with our manufacturer partners.

That's been a critical piece, but we do track the weekly system inventory and the forecast for production planning, all of that same information biweekly, and then the monthly production results. We're tracking filter failures and our outdate rate of leukoreduced products, which I have to say is extremely low.

The next couple of overheads address some of the issues that our organization is still wrestling with somewhat. So the customer issues that we're continuing to hear are that the increased cost associated with leukoreduced products is a major inhibitor for our customers, and they are continuing to -- Some customers, I should say, are continuing to have some resistance based on cost alone.

So we are trying to work with them as best we can. We are working with issues with the appropriate agencies on some of the reimbursement issues, but that's still an issue today for the

customers. It is a more expensive product.

Consumer demand: That has been a hard thing, really, for us to track, because we can do the best forecasting possible as we're meeting with our hospital customers, but if for some reason a hospital board or whatever decides that it's time for them to convert, their demand can change from one day to the next. That really causes some stress on the availability of filters and so forth.

The policy issues that we're still working with as an organization are, just an example of some of them: Whether to leukoreduce autologous units; leukoreduction of plasma is still something that has been discussed this morning and is also being discussed within our organization.

We do, of course produce and use SD plasma, and there are reasons why it is important that we should continue to look at the data, because we know that FFP does contain leukocytes.

Other issues -- and again, the QC testing. I think almost every speaker has addressed this issue. So I'm not going to go into more detail about that, but it is an issue that needs to be addressed.

The increased need for space: Again, some of our regions have actually been constrained in their

ability to convert because of their space issues.

Ergonomic issues: Strippers were a major issue, and we are, in fact, developing an ergonomically designed stripper to help that situation.

Filter inventory stockouts: I don't think we've ever gotten there yet, but it's something that's been at such serious levels that we have really had to track it almost on a daily basis.

The filter methodology we're looking at: There are two methodology types, in-line versus sterile dock. As I mentioned before, in our organization we use both methodologies at this point, and we are looking to use the most efficient methodology that's out there.

One of the other issues that we're still looking at is random versus single donor platelets, and just the basic cost of implementation. The regions that have size constraints, the amount of capital investment to make this possible is not insignificant.

Our inventory management during conversion: What we are finding is those regions that have gotten to around the 40 percent to 50 percent conversion rate have really found it difficult to maintain both leukoreduced inventory and, as we call it, a vanilla red cell inventory. So that's something that we're

working through as we go.

The recommendations that we -- and proposals that we'd like to make, I think, have already been heard today. So that's kind of comforting to know that everybody is experiencing the same issues.

Our thoughts are that we should move quickly with 100 percent prestorage leukoreduction of red cells and platelets. We think that it takes at least a year for organizations to make that conversion, and maybe more.

We'd like to hope that there is a way to decrease the QC testing involved with leukoreduction, and also we'd like to think that there's a way to fast track some of the filter reviews and approvals that the FDA is required to do.

So saving the best for last, our conversion status so far -- What I'm going to show you now is where we were in April of '98 and where we are or where actually as of October '99.

That's kind of hard to see, but where we were in October is 37.6 percent, and that's as a system. You can see here, in September is when the BPAC recommendation came out. We made our decision as an organization, and then the task force work began, and the ramp-up has been fairly significant.

So our target is to be converted by this date, and we've mapped it out that, in order to achieve that goal, this is the percent of progress that we're going to need to make on a monthly basis. Here is where we are with respect to that.

It's not too far off, and I have very strong reason to believe that, even in November, we're getting much closer to where we need to be to be consistent with reaching that goal.

So we're on our way, and I'll be happy to answer any questions during the panel process. Thanks.

(Applause.)

MS. CIARALDI: Thank you very much, Ms. Norrell.

Our next speaker is Dr. Heaton. Dr. Andrew Heaton recently joined the Blood Systems, Incorporated, as their Chief Medical Officer following an affiliation with the blood centers of the Pacific. Dr. Heaton was trained in medicine at the University of Dublin in Ireland, in pathology at the University of Cape Town, and in blood banking at Washington University in St. Louis, Missouri.

He has a research interest in component manufacturing, and currently serves as the head of the component group of the BEST Committee of the ISBT. I

was going to try to get in touch with him to know if that BEST meant "better" than something or -- I'm sure it's initials. Maybe you can tell us what it is.

Dr. Heaton will describe BSI's plans to move to universal leukoreduction. Dr. Heaton.

DR. HEATON: Thank you for the opportunity to speak at such an august meeting.

BEST stands for Biological Excellence for Safer Transfusion. Could I have the first slide, please.

It's my pleasure to report on the planning system that we've utilized at Blood Systems in order to implement universal leukodepletion. Next slide, please.

As part of my arrival at Blood Systems, we've established what we call a medical policy committee, which is a group of medical -- general medical physicians and research scientists who get together on a monthly basis to review medical/technical upcoming policy related issues.

So we met shortly after the BPAC recommendation and analyzed the medical questions, and we developed an opinion on the indications for leukodepletion.

We then proceeded to encourage operations

to validate both the sterile dock and the in-line system. We worked with operations to develop a cost versus volume, negotiated a revised process with our manufacturers, and then we made certain critical decisions for our operations.

We decided that our operational groups should be free to choose sterile dock versus in-line. We wouldn't mandate which they should use. We also decided that we would maintain bedside filtration filters to balance inventory during the transition process. Finally, we decided on central quality control, using the BMI device. Next slide, please.

With that in mind, the key goals of leukodepletion and the accepted ones that we felt were appropriate was the prevention of febrile reactions, avoidance of HLA immunization, avoidance of CMV infection.

We believe that the evidence for the reduction of post-operative infection was compelling and, as I'll show you later, we also believe that the quality of the red cells is significantly improved by prestorage leukocyte reduction. Next slide, please.

In terms of customer conversion then, we reviewed the attempts or plans to convert the customers, and we decided no mandates, that we wouldn't

order any customer that they had to go to leukodepletion.

We decided that we would implement a program of IND User, I-N-D, for transfusing MD education, and that we would provide a comprehensive briefing to our blood banks as we went through the transition process.

In order to facilitate it, we trained our regional management, both the technical directors and the executive directors of our centers. We restructured the price in order to facilitate the conversion and narrow the gap between leukocyte depleted and standard products.

We issued a newsletter. Our trade association, America's Blood Centers, has an excellent newsletter, and we supplied that to our customers, and we began a program of hospital visits with technical staff, physician visits by vendor and support personnel, and then our executive management visited administration.

So we visited the customer at three or four different levels. We also supported local seminars, focus groups, and technical advisory committee meetings as well in order to improve the knowledge. Next slide, please.

As we talk to the customers, there's generally concurrence that it does avoid febrile transfusion reactions to leukodeplete blood, and that it reduces HLA immunization, and it said most of our customers have increasing acceptance that there's equivalence in CMV reduction.

There is some residual concern of viremia versus reactivation, as some CMV donors carry the virus that are antibody negative. There's increasing acceptance of the post-op wound infection reduction indication, and certainly everyone agrees or increasingly they agree that it's convenient, and the consistency of product quality is significantly enhanced.

The question that the hospitals came back to us with, though, was is this a change in the standard of practice? Is it mandated? You did mandate things like p24 antigen, but you are not mandating the leukocyte depletion, and is there some significance to that difference? Can you prove cost effectiveness, and will it be acceptable for neonates to utilize leukodepleted blood instead of CMV screened blood? Next slide, please.

Well, then we began to look specifically at the different product lines, and the first is leukocyte

depleted platelets. The reality is most heme-onc patients may come up for transplant. It's well known now that 22 degree Centigrade platelet results in cytokine production and, therefore, reactions; and most, about 60 percent, of our platelet transfusions were already bedside filtered.

Bedside filter platelets were very expensive. So they are easily facilitated the conversion to leukocyte depleted product lines, because the difference in the new product versus t he old was much less when you added in the cost of the bedside filter.

Finally, the ease of technology access: The pheresis manufacturers have all produced very efficient leukocyte depletion SDP devices, and these facilitate -- The fact that it was so easily available facilitated a start with platelets. Next slide, please.

In 1997 and 1998, single donor platelets represented 66 percent of our total platelet doses. Now from our perspective, the transition from standard platelets to leukocyte depleted, we elected not to validate the leukocyte depleted random donor platelet filter.

There were concerns that it was expensive

and that it was an additional validation that we didn't have time for. So for us, the switch to leukocyte depletion also means a switch to pheresis platelets.

So when we talk here about this conversion, what we're saying is that 66 percent in those previous two years was pheresis platelets, largely leukocyte depleted, and the other third was random donor platelets and, therefore, leukocyte rich. So the priority was a focus on leukocyte depleted platelets, and you can see the LD/SDP as a percent of our total platelet doses. They were 66 percent in the two previous years, and they've gradually climbed to 77 percent across this year.

We also looked at our QC data, and we did approximately 2,000 QC samples using the BMI device, and only 0.7 percent fell below the 5 million times 10^6 standard, which I think is excellent.

We noticed -- This is the leukocyte count in the failures -- the average failure was 67 million, and there was a log normal distribution in the profile of the leukocyte failures, which I will come back to when I talk to quality control of leukocyte depletion. Next slide, please.

We then -- So the outstanding platelet issues then is that LD/SDP manufacture is far more

expensive than RDP manufacture. The switch to leukocyte depletion then pushes two extra costs on the hospital, both the leukodepletion cost and the switch to pheresis.

We believe that there is much that could be done to cut the cost of leukocyte depleted manufacture. The critical issue here is that Europe has largely converted to pooled buffy coat platelets for two critical reasons, one of which is that their regulatory authorities are much more sympathetic to pooling and to the use of the sterile dock device to allow pooling.

In Europe pheresis is relatively less common than pooled buffy coats, which are very much less expensive than leukocyte depleted single donor platelets. So one issue, we believe, that the FDA should look at is the FDA restrictions on pooling and the FDA restrictions on wet wet docks associated with the use of the sterile connection device. Next slide, please.

Switching to red cells, in the past red cells were basically boutique orders. They were special order manufacture, and so for us then the priority was manufacturing flexibility. The customer ordered. The customer didn't order, and we wanted to be able to have maximum flexibility.

The effect of that was that a very large percentage of our leukodepletion at the beginning of the year was by sterile dock, because that maximizes your operational flexibility. But as we increased our leukocyte depletion -- and this is our leukocyte depletion, the total red cell charges linked to the filter purchases -- it went from 17 percent to 42 percent across the year.

The fraction that we prepared by sterile dock came down, because it is quite clumsy to use the sterile dock in a manufacturing environment, and when they're offered the choice, your operating units prefer to use in-line systems, simply because they are easier to use and easier to build into the manufacturing process.

QC data was excellent. 0.4 percent exceeded the five times 10^6. The average leukocyte count of the failures was 21 million, and again there was a log normal distribution, which I will come back to later. Next slide, please.

Looking at the year 2000, our presumption is that many of the larger hospital systems will convert with our new contract year. There is no regulatory mandate. So at this point the hospitals don't feel obligated to convert.

There is no significant standard of care litigation or other reasons to make the hospitals go forward, and we believe that with continuing leukocyte depletion promotion and giving you the best guesstimate, we think that we will reach about 60 percent leukocyte depletion by the end of the year, and we believe that we will end up leukocyte depleting around 24 percent of our red cells by sterile dock, once we reach the fourth quarter of next year. Next slide, please.

Switching now then from market issues on to production issues, the sterile connection. The sterile connection is about a $2.00 premium for the cost of the device and wafer, and from a manufacturing perspective you offset the cost of this through avoidance of bad sticks, lab losses, test losses, and increased outdating through improvements to your manufacturing flexibility. But you do have additional instrument quality control, and you do have additional process quality control.

At the moment, the guidelines don't -- There is some guidelines on quality control of the sterile connection device, but they probably could be improved. There is also significant labor to perform the connection filter and relabel.

Critical question for us is: There is no definition of prestorage, and we believe that the FDA should identify -- and that this is a most important issue -- a standard for what prestorage means. So our suggestion is less than 72 hours.

Secondly, there is also a difference in the way that a regulatory agency treats the licensing of a device, via 510(k), versus a PMA, i.e., an in-line filter system. We believe that it would be helpful if the licensing of these two could be standardized. Next slide, please.

Whole blood filtration: Well, it's much more convenient. The containers come pre-labeled. Manufacturing is simple. The plasma is leukoreduced, which is not with the sterile dock device.

We believe that an increased hold period might enhance phagocytosis and, therefore, reduce bacterial contamination and, as I will show you, 4 degrees Centigrade filtration greatly prolongs the process. So from an operational perspective, your operating units are desperate to filter at room temperature and not filter in the cold.

In the regulatory process, the questions, I think, that need to be asked is: Would a minimum hold decrease bacterial growth? Could we prolong the period

of hold to increase presumably phagocytosis and subsequent removal?

If 22 degrees Centigrade products are comparable to 4 degrees products, we would very much like to be able to hold the whole blood at 22 degrees Centigrade, at least for eight hours, if not overnight, in order to cut our manufacturing costs, and the 24 hour hold is standard in the rest of the world.

The last question is: Is blood mobile filtration acceptable? Once you collect the unit, can you just mix it up, turn it upside down, break the seal and filter it on the mobiles, because again that would convey very significant operating flexibility. Next slide, please.

The advantage then of whole blood is you don't have to centrifuge and filter. You do have a problem with whole blood in that platelets are nearly always slightly activated by phlebotomy, and certainly, consistent leukocyte reduction requires platelet removal.

So the penalty that you pay as you switch into in-line whole blood systems is that you don't have any random donor platelets and, therefore, you are forced to convert to single donor platelets with all the associated cost implications of that transition.

The effect that has is that we are now desperate to increase our single donor platelet production, because we now have to meet all the needs that used to be met by random donor platelets.

That's going to place pressure on the need to increase the number of donations per year and, in addition, our customers are beginning to get anxious over the number of platelet products we're splitting, because the average content of the average pheresis product is coming down as we more aggressively split products.

So one of the issues we believe the agency should carefully consider is the effect of leukocyte depletion on the single donor pheresis regulations, the frequency of donation, and the long term implication that it will push or drive multi-component apheresis. Next slide, please.

The current reservations that we most frequently hear then are the CMV question on wound infection -- is it really true? Now hospitals push us: Won't you please prove cost effectiveness. They ask why must we switch to single donor platelets; can't we get our random donor platelets that were inexpensive?

Lastly -- and this is a new bureaucratic

trick -- the hospitals have started saying, well, if it's not a change in the standard of practice, and if the FDA doesn't mandate it, we are defrauding Medicare by supplying a leukocyte depleted product unless the physician writes an order for leukocyte depleted products on every single order he makes.

That is a significant issue now for the more aggressively cost oriented hospitals. Next slide, please.

Well, moving on to production variables. As you know, I'm very interested in the technology of manufacture, and I'll show you a couple of issues, but many things affect the quality of your leukocyte reduction, the capacity, your temperature, your whole blood versus ASRVC filtration, your filter height, filtration speed which will have some effect in your complement of kinin activation. Next slide, please.

Now these are studies that were done in my research lab with the American Red Cross, and I show them to emphasize the very significant difference between filtration at 4 degrees Centigrade versus filtration at 22 degrees Centigrade.

On average you get one log better leukocyte reduction. In this system, which was the PALL RC-300 filter in-line, none passed the 5 million limit, but

there is a significant difference. You can see the implications of the conflict between the production staff, who want room temperature filtration, and the product quality people like me who want 4 degrees Centigrade filtration, because you get a more consistent product. Next slide, please.

We also observed that there is an improved -- slight improvement in red cell quality. Post-transfusion recoveries are about three percent better, and all of the groups that have studied leukocyte reduction, as the quality of the leukocyte reduction improved, the degree of improvement in red cell quality was quite significant.

You will observe this most dramatically if you look at the hemolysis in the units. It is significantly less in prestorage leukocyte depleted units. Next slide, please.

If you look at platelets, we've done a series of studies. In this case, these are paired studies where we did tests and control, and we did the same donor with leukocyte rich platelet products and leukocyte depleted platelet products, leukotrap, buffy coat and pheresis, and you'll see that there is no significant effect on the quality of the platelet as a result of the leukocyte depletion technology.

So we felt that there were no manufacturing issues in terms of platelet quality. Next slide, please.

Then we began to look at the details of manufacturing and the quality control and the statistical process control needed to back up your leukocyte depletion system. At BCP we are the coordinating center for the VATS study, and we have developed a PCR based method which will allow us to quantitate leukocytes down to the 10^3 level in the containers.

In essence, we have primers that are primed with the DQ alpha gene, and we use PCR to grow up the DQ alpha segment in the leukocytes, and we use that to quantitate the level of leukocyte contamination. Next slide, please.

In this study there were 11 centers that performed leukocyte depletion. QC was performed on every single unit that was transfused, and you'll notice a few things that drop out that are quite interesting.

Basically, all met the current standards, with a few outliers that meet the current specifications. But the in-line systems here where filtration was performed at 4 degrees Centigrade

performed more consistently and with less outliers than the whole blood systems that were performed either at 22 degrees Centigrade or in a less structured fashion than these three particular laboratories. Next slide, please.

So leukocyte residual count is minimized by a hold filtration time significantly shortened by room temperature filtration. The current regs, though, if you read them, imply that you should be cooling your red cells as fast as you can to 4 degrees Centigrade, and yet your production people -- that's the last thing they want to do in order to speed up the filtration process.

So we would like the FDA to consider classifying prestorage to 72 hours, increase the 22 degrees component hold time to 24 hours, and there are some manufacturers' instructions issues which I will come back to later. Next slide, please.

Now when you look at what actually happens -- this is now the VAT study, compiled in a single group, and this is the log residual leukocytes, and you'll observe that on a log normal basis you get a nice bell shaped curve.

What you should actually be drawn to are the little blips out here. In practice, it's our

belief that the failures in leukocyte depletion probably are a separate subpopulation. Now this is not a continuous distribution, but rather it is a bimodal distribution of one population of normals and a separate population of abnormals.

If you apply that statistical model -- next slide, please -- to the sampling frequency that you need, you can identify the size of sample that you will need in order to pick up that subpopulation. This becomes especially important, because in the United Kingdom and the Council of Europe there are requirements that the one percent or four units per month is relatively common standard; but unlike this country, they don't demand 100 percent pass.

In fact, there is a 75 percent requirement in the U.K. and a 90 percent requirement in the Council of Europe standard.

Now if you apply the bimodal approach to quality control -- next slide, please -- you will see that, in order to have a statistically valid chance, a 95 percent chance, of picking of five percent outliers, there is a standard probability curve which allows you to calculate the sample size that you need.

Our estimate was that, based on the average counts of the leukocyte depleted failures, a blood

center would need to count 40 samples in order to have a 90 percent chance of picking up ten percent failures.

So as we look at QC, we believe that the agency should consider the statistical basis on which leukocyte depletion fails, and then develop a statistical model that would apply specifically to that failure profile, rather than applying a one percent or a four per month.

Four per month would be inadequate to detect a bimodal failure, but one percent per month is a very large and burdensome requirement that would not necessarily meet the goals of the leukocyte depletion system. Next slide, please.

So what we would suggest is a validation sample of 40, followed up by samples of six. The 40 will allow you to pick up both the unimodal and the bimodal distribution, and a routine sample size of six per location would give you a very good chance of picking up a unimodal shift.

The concern is that, if you push your standards too hard, your beater error, your chance of identifying an error when one doesn't exist goes up very dramatically; and in leukocyte depletion, since the filters perform so well, there is a very high beater error, because it is very easy for a single

outlier to extrapolate into a perception of QC failure when, in fact, that does not exist. Next slide, please.

So in terms of product issues then, different systems have different performance characteristics. We believe the user should validate against the defined standard. The QC should be adequate to detect deviation, and we believe the system performance must be judged against clinical criteria rather than against statistical criteria.

So a recommendation that the manufacturer should supply a reference database of how their system performs so that an operator can compare their performance with that of the reference database.

We believe that minimum validation standards should be part of all 510(k) PMA or NDA instructions, and that the one percent or four per month standard requires review. Next slide, please.

Moving on to -- Can we go on to the next slide? I'll skip that one.

So in conclusion then, we believe that we've had an effective program for implementing leukocyte depletion. We believe that, if we offer the hospitals the choice, that we should be able to relatively easily get to around two-thirds leukocyte

depletion, but that in order to exceed that level, we will need some form of additional guidance or mandate or very strong recommendation from the agency.

Secondary, we believe that the agency could facilitate our activities by providing amended QC guidelines that are more orientated toward the failure distribution profile of leukocyte depletion systems.

Lastly, we believe that the agency could help us with costs, if it would amend some of the regulations related to component manufacture, specifically focusing on pooling and the time to leukocyte depletion.

Thank you.

(Applause.)

MS. CIARALDI: Thank you very much, Dr. Heaton. You probably were wondering where my cane was, because we are a few minutes past. All the information has been so interesting that I just left it on the floor.

For our next talk, we'll be getting two for t he price of one, essentially. Both Dr. Bianco and Mr. MacPherson will talk. I'm going to introduce them both at the beginning.

Dr. Celso Bianco joined the New York Blood

Center in 1983 and is currently the vice president for medical affairs at the New York Blood Center. Dr. Bianco is a former assistant professor at New York University School of Medicine and Rockefeller University and a former professor of pathology at the State University of New York in Brooklyn.

He is also the President of American Blood Centers. Dr. Bianco will be speaking today on the efforts of ABC's members to implement leukoreduction.

Following Dr. Bianco will be Mr. Jim MacPherson, the Executive Director of American Blood Centers. He will present ABC's position on a universal leukoreduction.

Mr. MacPherson has held the position of Executive Director since 1986. Previously, he was director of hemopheresis, regulatory affairs and operations research for the American Red Cross in Washington, D.C.

Mr. MacPherson holds two Master's degrees, one in cellular physiology form GW University in D.C. and one in pathophysiology from the State University of New York in Buffalo.

Dr. Bianco will start the ABC's presentation. Thank you.

DR. BIANCO: Well, thank you very much for

the opportunity to be here. My presentation -- Our presentation, actually, will be kind of different than what the other presentations were this afternoon. I think that we got enough of the technical aspects of it.

What I'm going to try to do is a little bit -- is to talk a little bit about the premises of leukoreduction, to review with you the status of implementation among ABC centers, to talk about some of the implementation issues, and ultimately where do we go from here.

Why, I think, is very interesting. We have been trying to justify it in costs and all that, but that has been the history of our life in what we do. The purer, the better. We start with whole blood. We went to packed red blood cells. We started with random donor platelets. We went to apheresis. We started with cryo, went to crude Factor VIII, went to monoclonals.

The science also has supported, as was very well discussed today, some of the indications for filters. We have had also many years of experience with bedside filtration -- positive, but very variable, depending on the performance of those filters and on the difficulties that were associated with their use.

The introduction of apheresis platelets created a rather cost effective system for the introduction of leukoreduced products, because they didn't need filters. They didn't need the labor associated with that leukoreduction.

The problems that we have is that we have in recent years, because of the substantial cost associated with leukoreduction -- essentially, a 25 percent increase in the cost of manufacture of these components -- that none of the cost/benefit studies that came out so far or that have been discussed are really convincing, and I have the impression that that study about cost/benefits will never be done.

Finally, the mythology has moved several countries around the world to introduce leukoreduction, and if it is for folklore, maybe that's something that we should do.

Among ABC centers, the numbers that I am going to provide you are based on a survey of ABC member centers. The survey was completed a few days ago, a week ago, and at that time 57 members had responded out of the 72, almost 80 percent. Actually, we had two more responses that came later, and then so I did not incorporate them here.

If we talk about single donor platelets, the vast majority of the centers that are included in the survey provide most of their platelets as leukoreduced platelets. There are centers all over the range, but essentially platelets -- single donor platelets are not the issue, essentially, of what we are discussing today.

If they were to replace the current use of random donor platelets as some speakers have discussed before, this would be a big issue. The real issues are in red blood cells.

Among our member centers, among these 57 centers, the majority of the centers leukoreduce less than half of the products that they distribute, and you'll see that the peak of distribution is in centers distributing around 10-25 percent of their red blood cells as leukoreduced products.

When we talk about random donor platelets, very few of the centers are distributing -- Actually, only two of these 57 centers were producing random donor platelets that were leukoreduced for distribution to their customers.

The plans for implementation that our members have: Very few centers are done. They have -- Two of our centers have totally seroconverted --

Seroconverted? That's a real Freudian slip. Two of our centers have totally converted their products to leukoreduced products.

Another center, a major center, is on January 17th, all the products that they are going to distribute will be leukoreduced products to their hospitals in a major city in the southwest.

Forty percent of our centers have made plans for implementation and are gradually executing those plans. However, half of our centers are not at this point considering leukoreduction.

As we asked our centers for how they plan to do it, most of them are being very careful in their plans for implementation, but as I mentioned a minute ago, a few of our centers have come with a real specific date for the implementation of leukoreduction. However, most of our members have been in very intense discussion with our hospitals or the hospitals that we serve in terms of how we would do it, what are the issues, and trying to bring the hospitals up to date on all the information that is available for this type of activity.

There are many implementation issues. Many of them were discussed in excellent ways. So I'm going to go, more or less, quickly. I'm going to try to

compensate for the time that Dr. Heaton stole from us.

In terms of indications, I'm very disturbed about some of the discussions about plasma and leukoreduction. We knew for many years that plasma has some red cells.

There were some interesting abstracts from Dr. Holland's group at the last AABB meeting, but I don't think that we have, at least at this point, sufficient amount of clinical indications to really go heavy on that sense. I think that we should pay attention to the products for which we really see that the most benefit will come to our patients.

In terms of technology, we heard about the two major methods, and that's a difficulty that most of our centers are having in terms of choosing the in-line versus sterile docking.

In-line is a very interesting system. However, the losses associated with the number of units that are not utilized because the donors are deferred or tests are positive or problems occurred during the manufacture, because they don't meet the release criteria.

Sterile docking is very labor intensive. You need separate filters, and the question of labor and space is also very important.

QC: We had a lot of discussion today, and I think that we feel that we are all going on the right track.

There are two issues that are very, very important. One of them is the sickle cell trait. Some of the speakers prior to me mentioned that units with the sickle cell trait will not filter adequately. About one in 400 black -- African Americans have this sickle cell -- are homozygous, and about ten percent of African Americans have this sickle cell trait.

So that's a substantial issue for the African American community, and we will have to find actually, I hope, ways to deal with these issues in terms of we need to increase the number of minority donors.

We are looking for them, and at the same time, we don't want to see a procedure that we introduce being an important obstacle to having these individuals participating of the donation process and actually providing many of the rare units that we are looking for in terms of use or even piece that are less frequent in other ethnic groups.

Again, another product that is somewhat threatened by leukoreduction is source leukocytes. Just in research we -- for research, we produce an

immense amount of leukocytes to universities and clinical laboratories in New York.

There are some companies that manufacture products that are based on source leukocytes. If we go to in-line filtration, source leukocytes disappear, at least if they continue being manufactured as they are being manufactured today.

In terms of logistics, we will have to increase personnel. We will have to have bigger cups in our centrifuges. We will need more space. We will need hangars.

I like the cart that the Red Cross has. The people that are doing this study with us have suggested that we buy these things that they have in cleaners so that the unit enters in one side, and they go walking around the room to come out on the other side, and we are going to compete with the diaper industry in terms of generating biological waste.

Again, a timeline is something that is very important, and we hear the discussions. We have to have time to availability of filters, training, validation.

We hope that Captain Gustafson is going to make licensure very easy for us, and maybe -- I really like the idea of utilizing the new approach of the

monograph and maybe making the process easier for introduction into several centers, and we have tim for that.

We discussed extensively the accepted indications, but we have to recognize that these accepted indications really represent about 20 percent of usage of blood currently, of red blood cells and platelets. To extend that to universal leukoreduction, we have many steps to go.

I think that we are in synch, and from what we heard today here, everybody -- either some of the people are already there, and other people are a way getting there. However, I think that we have a serious disassociation of our thinking with the thinking of our major customers, the hospitals.

The hospitals tell us that costs are unacceptable, that leukoreduction, universal leukoreduction, is unaffordable, that they cannot do it without adequate reimbursement. They tell us you cannot impose leukoreduction, because you do not have an FDA mandate, and this is not a standard of care.

They raise questions about the medical benefits beyond the patient groups that we clearly discussed here today, and they also discuss about question of costs/benefits. They don't believe in us

when we tell them that in-hospital times and admissions and all that will be shortened and that their costs will go down.

Finally, I think that they really resent that they have not been part of this process. We have been evolving our thinking toward leukoreduction as a natural process. We have not been able to bring all those participants of the health care system to come with us.

We will try to propose a solution, because that's a real conflict to you. But I have to tell you that a few days ago during Thanksgiving, I went to visit my closest friends to spend Thanksgiving with them in a small town in West Virginia, and I found a sign that really represents the situation where we are.

Since we are somewhat confused, I have asked Jim MacPherson to come and present to us the position of members of America's Blood Centers. Thank you.

(Applause.)

MR. MacPHERSON: Thank you very much. I will try not to duplicate anything, and try to be very brief. I appreciate the opportunity.

The position is pretty simple, and that is: When, and as required, the members of America's Blood

Centers, which represent about 6.7 million donations or about half the blood supply, they will participate and comply; and as Dr. Bianco said, most of them are already in some kinds of planning stages already.

Now we've already heard about the patient outcomes that may offset costs, but these are all inconclusive, and I think -- You know, Jong Lee said, you know, don't talk so much about money; talk about implementation issues. Well, it's all about the money.

What we're talking about here is a cost increase to the health care system of in the neighborhood of half a billion dollars. As Everett Dirksen -- or to paraphrase him -- once said, you know, 100 million here, 100 million there; pretty soon, you're talking real money.

Without the data to support this, this is a very, very hard sell for hospitals. This is the back of an envelope calculation, but it does include a lot of things that have been talked about here, one of the things that Dr. Heaton emphasized, talked about, the loss of random platelets to go into single donor platelets.

That's not only a loss in terms of -- or not a loss, but an increase in cost, but it's -- to the blood centers, it's a loss margin that subsidizes the

price of red cells. It doesn't cost $40 to $50 to produce a unit of platelets. Everyone knows that, but there is a huge margin built into that that subsidizes the price of red cells.

When that's gone, that has to come from increased fees for red cells. So when we're talking about passing along the cost of leukoreduction, that's a hidden cost that a lot of people don't directly address.

Now the big problem, of course, is reimbursement. If we all got paid for it, we wouldn't care. But we know today, the way the health care system is set up, there is a two to three year delay in adjustments to Medicare and Medicaid payments under the DRG system. Of course, most transfusions take place on in-patients and take place under the DRG system.

That's just the way the system is set up. So when you start talking about putting something in place that's going to start costing a half a billion dollars a year, that's a lot of money to pass along to the hospitals in general, especially if they don't know what the offsets are.

Second, it also shows up specifically in one budget in the hospitals, and that is the hospital laboratories.

Now Medicare and Medicaid, we know, also pays. They're the lead dog here, because they pay for well over half of all transfusions that take place. Now HCFA has the authority to fix this. They don't need Congressional help on this. There are ways that they can do this themselves.

There are some simple fixes that would reduce the two to three-year delay down to maybe one year, and those have been proposed to them. There's also carve-outs, if they would be interested in doing that, and as Jay Epstein said this morning, there's some active discussions going on within HCFA to try to figure out how to do this.

You solve that problem, and much of it goes away. Now you still haven't proven that you've improved the out-patient outcomes and saved the money, but at least in terms of the hospital blood bank and the blood center, you've paid for what you're doing.

So our recommendation is that, when FDA has a recommendation like this -- and in the future, too because most of the new technology that you're looking at that's going to come down the pike is going to be a whole lot more expensive than adding two to three dollars on for tests. That was a big chunk to add, about five percent of the cost, but now you're talking

adding 20 to 25 percent cost.

We're talking about other technologies in the future in terms of viral inactivation that are going to double or triple the price of blood. So you can't have two to three-year delays when you try to talk about that.

So when FDA starts coming out with these kinds of recommendations, we say, hey, you're part of HHS. You ought to talk to the other side, and you ought to coordinate your activities, and there should be some kind of joint approach to assuring that the reimbursement is there when the recommendation comes out.

In terms of implementation period, other people have already addressed this. So I won't belabor this issue, but obviously, the reimbursement concern is the big concern for the hospitals and for the blood centers.

It's a manually intensive process, as you've seen by everyone. It requires that you hire staff, train staff, put new quality process control procedures in place. You heard this morning there's the problem of the availability of filters, that there may not even be enough filters to go to total universal leukoreduction until the end of 2000.

A shortage of platelets, if we had a very short phase-in period, because it's just impractical to replace 4-6 million random platelets with the million or so pheresis platelets that you would need to perform -- platelet pheresis procedures, that there's a huge gear-up for that.

So we recommended and are glad to see that FDA is thinking along the same lines of a phase-in period perhaps for three years. Those communities that want to do it now, want to do it tomorrow, want to do it next week, if they are comfortable with that, that's terrific. For everyone else, let them have some time to try to work out some of these logistics as other problems go and to solve some of the problems that we've all seen today.

In terms of logistics, all of this again has been talked about before. You need flexibility in this process, and again we're real pleased to see that FDA, between a choice of bad and awful, they're giving us the choice of bad.

So we would just as soon like to see as much flexibility as possible in terms of this, and not to be very specific on how it's done, and with their oversight and guidance I'm sure they will make sure that we do it right. But again, leave the details to

be worked out between the vendors, the blood centers, and the hospitals. Thank you.

(Applause.)

MS. CIARALDI: Thank you very much, Dr. Bianco and Dr. MacPherson.

All right. Our next presenter is Dr. Menitove. Dr. Jay Menitove is the Executive Director and Medical Director of the Community Blood Center of Greater Kansas City.

He is also a clinical professor of medicine at the University of Missouri, Kansas City, and at the Kansas University School of Medicine. He is board certified in internal medicine, hematology and blood banking.

Currently, he is the Chair of the AABB standards committee and is on the board of directors of America's Blood Centers. Dr. Menitove will talk about community blood centers leukoreduction implementation plan. Dr. Menitove.

DR. MENITOVE: Thank you very much, and thank you for inviting me to the presentation workshop.

What I'd like to do is to present a summary of our experience in Kansas City. Just to show you where we are, we're in the heart of it all, right in

the middle of the country, and are actually a combined program now of the Community Blood Center and also the Kansas Blood Services in Topeka.

Our current volumes of collection for this year are about -- Our current collections are about 113,000 units per year, and we're producing about 8500 single donor platelet preparations, of which most are leukocyte reduced, about 27,000 random donor platelets, 37,000 units of fresh frozen plasma, and about 4,000 units of cryoprecipitate, just to give you a sense of what we've done.

Now similar to some of the data you've seen before, in the beginning of 1998 about ten percent or so of the units -- a little under ten percent of the units leaving the blood center went out as leukocyte reduced.

In June of 1998 one of our hospitals decided to go to 100 percent leukocyte reduction, and then subsequent to that, and actually slightly -- a couple of months after the BPAC meeting in September of '98, the usage continued to increase -- that is, the switch to leukocyte reduction increased.

Initially, our approach was to use sterile connection devices for making leukocyte reduced red cell components, and that did, in fact, require that we

add a third person or an additional person on the third shift.

Subsequently, we thought we would be switching to in-line filters, presumably because they're more efficient, and the target, which is really a typo there, in our thoughts was that we would go to about 50 percent sterile connection, about 50 percent in-line leukocyte reduction.

By doing that, we would save the cost of the third bag. So we would only have a double bag configuration. In-line would allow us to do leukocyte reduction on second shift, but we would lose the random donor platelets.

The components laboratory, on the other hand, felt that the sterile connection facilitated inventory management, and in-line filters -- in terms of looking at the mix when we made decisions about that, decided to go with a single whole blood filter rather than a dual process where thee would be multiple filters involved.

Predominantly, that decision was made, because the multiple filter system was felt to be cumbersome, would require a change in the centrifugation buckets, and that was felt to be a lesser desirable option.

The whole blood being filtered prior to the centrifugation also, we felt, was helpful in terms of just logistical approaches to what we were doing.

So as you can see, we started -- and I just want to concentrate on this part of the curve -- saw an increase in leukocyte reduction to approximately about 30 percent of production by December of last year. At the same time, we saw the need for random donor platelets decreasing.

That was at the same time we decided to start up going with the in-line filter process, and we did that, actually, at higher than the initial target and, I guess, the first month made about two-thirds of our needs in leukocyte reduced red cells using the in-line approach.

What we found was that the demand for random donor platelets increased at the same time that we had made the switch. So we backtracked what we did, and actually the curve reversed. So that we're back using mostly sterile connection filtration at this point in time.

We've also seen a slight increase in the use of leukocyte reduced units subsequent to that time, about 35 percent. Actually, currently we're a little closer to 40 percent of the units collected as

leukocyte reduced units.

Some of the issues are: Can we manage our ABO mix in terms of providing enough leukocyte reduced units, and are we able to make enough random donor platelets, again similar to some of the comments you've heard before.

At about a 35 percent rate of leukocyte reduction for red cells, our thoughts are what do we do if it increases towards 100 percent. The initial plans are to increase the use of in-line filters. We could do that on the second shift.

We wouldn't need additional staff, and again we would have the advantages of reducing the number of bags that are there to a double configuration. However, we feel that the limit of using the in-line approach is 50 percent.

We hit the wall at about 50 percent leukocyte reduced red cells, and that's related t our current need for producing random donor platelets. Now if that were to change, then, obviously, where we hit the wall would change, but that's about what we're making today in terms of random donor platelets, plus making some cryoprecipitate and quad preparations for neonates.

So we think that's probably what's going to

-- where we're going to have to make additional decisions. The options are to increase sterile connections -- that would require us to add an additional staff person with a cost associated with that -- or we could go to 100 percent in-line filtration plus converting all of our platelets, the single donor platelets, which we don't believe will be accepted by the physicians and hospitals, or we could use specific red cell and platelet filters.

We have not made any decisions about that. So that's where we stand at the current time. Now just for -- Dr. Lee asked -- allowed me and asked for suggestions for the FDA, and just a few comments.

In terms of a conceptual approach, one way of looking at what we've done with blood safety is donor deferral, screening process, inactivation and removal of pathogens.

So looking at it in a triad type of way, perhaps one way of looking at leukocyte reduction is the scientific basis, and we've heard comments about that, then an implementation plan. Then, unfortunately, reimbursement does become an issue and cannot be avoided.

I believe we should be looking at evidence based decision making, and I like Celso's slide of the

two arrows converging on each other. I think this is very difficult, and my own personal belief is that we're in a time of incredible flux, and I have changed my mind on this subject probably more than any other in terms of the value of going to universal leukocyte reduction. But if there is a scientific basis and it is based on evidence, we can then do professional education.

I think that, if the data are there, it would be accepted. Then going the next step, to reimbursement education, would be a natural step.

In terms of implementation, I've kind of bifurcated this into two options that blood centers can follow. One is to take a responsive stand, and the other is to take a directive one.

We have chosen to take a responsive stance. That is that we'll see if the evidence is out there to make a decision. If it is, it allows for educated decision making; and if it's supported scientifically, we believe the trend will move in that direction. So the train will follow the tracks that they ought to follow, presumably.

The opposite stance is one of a directive approach where you have standardization presumably to achieve economies of scale, and in all fairness, that's

probably where the trend is taking us anyhow. So you can get there faster. But as I said, we prefer to take the responsive one.

So what have we found? In our area, we really see a bimodal distribution. What I put on the y axis is the number of hospitals; on the abscissa, the percent that these hospitals are using that are leukocyte reduced.

So hospitals -- More than 30 of our 65 -- or actually 70 hospitals are accounting for 41 percent of the red cells that are transfused, use somewhere between zero and five percent leukocyte reduced red cells.

On the other end of the spectrum are hospitals accounting for -- about 15 or so hospitals, accounting for 31 percent of the red cells that are transfused in our area that are using close to 100 percent leukocyte reduction.

Then we see a few hospitals that actually account for a large percent of the blood transfuse using somewhere between 15 and 20 percent of the leukocyte reduced red cells.

So my sense is that this really is a bipolar distribution, either none or all, and then a few hospitals using about 15 to 20 percent leukocyte

reduced red cells, and when asked, the comments that I get are that the red cells that are leukocyte reduced in those hospitals are used by oncology patients and a few of the anesthesiologists are using -- are ordering those leukocyte reduced red cells.

Now I can't help but come back to an issue of reimbursement. The health care triad is the quality, access, and cost. In this arena we do have to talk about reimbursement.

From a personal point of view, I am not certain that this is the best way to spend a half a billion dollars in a zero sum type of environment. There are clear advantages.

If they are supported scientifically, then I think it makes sense, and I think that if it really -- some of the data that we really head are correct, in the long run there may be some reimbursement savings or cost savings to the hospitals. But the reimbursement issue is a very significant one.

When I've spoken to pathologists in our area, they particularly wanted me to dwell on this for a moment, because they are facing enormous pressures from their administration.

To go along with what others have said, if there's an FDA mandate or if it becomes t he standard

of practice, then they will obviously move in that direction. However, in a time of indecision they are going to wait and see what happens, and this is a factor in that decision making process.

Thank you very much for your attention.

(Applause.)

MS. CIARALDI: Thank you, Dr. Menitove. Our last speaker is Dr. Dennis Goldfinger of the Rita and Taft Shriver Division of Transfusion Medicine of Cedars-Sinai Hospital.

Dr. Goldfinger is also a clinical professor of pathology and laboratory medicine at UCLA. He attended medical school at the State University of New York in Buffalo and followed it up with studies in clinical pathology at UCSF and a fellowship in transfusion medicine at NIH.

Dr. Goldfinger will talk about the experience of his hospital with universal leukoreduction and what has happened since then. Dr. Goldfinger.

DR. GOLDFINGER: Thank you, and I'd like to thank the Food and Drug Administration and their staff for inviting me today. I would also like to thank Dr. Menitove for catching us up, so that I've only lost half of my allowable time to give this talk.

What I'd like to do today is discuss with you some historical perspectives of Cedars-Sinai and my own involvement in leukocyte reduction, talk about our own experience in attempting to accomplish this goal, and finally to try to tell you how I think you should not attempt to achieve the goal of universal leukocyte reduction.

First of all, after 25 years of trying to convince the rest of the world that leukocyte reduction would be a good idea, I can't resist the opportunity to say I told you so. So I'm going to show you four old slides.

You can see that these are old, and they were actually made in 1980, just to point out that the same kinds of issues that we discussed then are the very same issues that are the hot topics right now.

First of all, a study that we did in the late 1970s looking at the incidence of transfusion reactions, nonhemolytic transfusion reactions. We followed about 10,000 transfusions and found that there was a significant reduction in the incidence of all forms of nonhemolytic transfusion reactions in patients who received, in this case, saline washed red cells.

We also talked about infectious complications and recognized that perhaps the removal

of leukocytes from blood might reduce the risk of transmitting agents that were carried in peripheral blood leukocytes like cytomegalovirus.

Also we talked about alloimmunization to leukocyte and platelet antigens and the impact that that might have on patients who were to receive platelet and granulocyte transfusions.

Finally, we recognized that substances that accumulated in blood during storage might be harmful to the recipient. In those days the word cytokine was not known, but as you know, there is concern that these kinds of things do impact on the quality of the transfusions that we give.

Now so much for ancient history. I'd like to tell you about our experience in achieving the goal of 100 percent leukocyte reduction. We did this for two years, beginning in 1992.

This decision to deliver this was based upon two premises. First of all, that the passenger leukocyte, as Dr. Harvey Klein has referred to these, could not possibly benefit the recipient of a blood transfusion, but might cause harm.

Secondly, unlike some others, we believe that febrile nonhemolytic transfusion reactions are not something to be ignored, and that are potentially a

serious problem.

We did not believe in this approach of waiting until patients had adverse reactions to blood transfusion, to transfusion of ordinary nonleukocyte reduced components, before switching to a leukocyte reduced product or, even worse, using a rule of two or three, waiting until the patient had two or three adverse reactions before giving the better product.

This is kind of a preventive therapy, and it kind of can be -- We could use the analogy of a drug, which is something that the FDA, of course, is more used to regulating.

If we had a new antibiotic, for example, a new cephalosporin, and this was a highly effective antibiotic but it caused adverse reactions in one to two percent of recipients, and we had another preparation of that same antibiotic. It was just as effective, but it caused no untoward reactions. Which one of these would we choose to give? Certainly, which one would patients want?

I think, in a regulated environment, we would not even be able to allow to market the less safe material. This is the same kind of thinking that we applied to leukocyte reduction.

This effort -- First of all, we recognized

that washed cells were really not happy cells, and that it was impossible to achieve the goal of leukocyte reduction with saline washing. But of course, filtration allows this to occur.

This was a multi-focal effort. It required the participation, first of all, of our community blood center, the American Red Cross in southern California, along with the Palm Beach blood bank from which we were getting a significant amount of blood.

They would prestorage filter all of the blood that they sent to us. We have a collection facility that collects about a quarter of the blood that we transfuse, and we did prestorage filtration on all of those.

We also filtered in our component lab all red cell units that did not come to us already filtered. This represented a small number of units, like directed donor units that came from other centers. Finally, on the nursing units nurses performed bedside filtration on all units of platelets.

Some statistics here. First of all, we used only single donor platelets in those days, which is what we use now, and I'll talk to you a little bit more about that in a moment. But all of these units, about 2500 units a year, and they were filtered all at

the bedside.

We were transfusing in those years about 22,000 units of red cells per year, and as you can see, they were all filtered, most of them, prestorage.

There are real advantages to going to 100 percent or to universal leukocyte reduction. Now, clearly, the downside is that there is increased cost. On the other hand, inventory management is really a cinch. There's only one kind of component. It's all leukocyte reduced. So that the technologists in the blood bank, the nurses dealing with this, love this approach.

In addition, clinical decision making is also made very easy. All patients receive leukocyte reduced components. So that all patients are getting the same thing, and I think in this case all patients were getting the best thing.

Now in 1994 we abandoned this project, and we did it because of a need to reduce costs. We've heard -- Many times over the years I've heard that Cedars-Sinai is a so called boutique hospital, and it really doesn't operate in the real world.

Well, of course, that's a ridiculous statement. We get paid the same way that every other hospital gets paid, Medicare, private insurance and, more and more, capitated contracts. So there's really

no difference in the way we operate and the way everyone else operates. However, in these years -- this is 1994 -- we were facing serious cost constraints.

In the case of the laboratory we lost 25 percent of the individuals who worked in the laboratory, from over 400 people to just around 300 people. This was a huge cut. After 20 years of trying to convince unsuccessfully the rest of the world that leukocyte reduction really made sense, we had to kind of throw in the towel here and say that we could no longer justify losing personnel while we're trying to maintain an inventory of only leukocyte reduced components.

So we stopped doing it, and we went to doing what most of you all do, and that is leukocyte reducing on demand. Right now we probably transfuse about a quarter of our units of red cells in a leukocyte reduced form.

Now finally, I'd like to discuss with you what I believe you should not do in order to achieve this goal, and what you should not do is reverse the accomplishments of 50 years of transfusion medicine progress, things like autologous transfusions, single donor platelets, reducing donor exposure or resisting

new developments like safer plasma.

I'm dismayed to hear more and more, really, I think, excellent people coming from fine institutions talking about doing this sort of thing. Our journals are filled with articles, typically mathematical models, that suggest that these kinds of technologies are not so called cost effective.

Autologous transfusion: This is pre-deposit autologous blood prior to surgery. Clearly, this was a great boon to patients in the early 1980s during the AIDS epidemic, and it's clearly the choice of patients. We do this, and we think it makes sense, but it is a more costly kind of technology.

Single donor platelets: This is an unbelievable one, to me, because there is -- How anybody can argue in favor of the use of pooled platelet concentrates is just beyond me.

Yet we're hearing from more and more institutions that they think it's a good idea, and it's one of the ways that they're going to justify the use of universal leukocyte reduction, and that is to go back to pooled platelet concentrates.

The only reason for doing so would be increased cost. Clearly, if there's any product that should go the way of fresh whole blood, it should be

this product, this 30-year-old, outmoded product that, in my opinion, represents a clear and present danger to the American public. We'll come back to this in a second.

Now the supposed justification, of course, is that blood is so safe that we need not be concerned. Now most unbelievably, I think, recently we're seeing articles suggesting that we no longer have to protect our children from blood, that programs for neonates that minimize donor exposure can be abandoned, because they're really not cost effective.

Now, of course, the patient doesn't seem to have any say in any of this kind of decision making. Well, very often transfusion medicine physicians seem to see their role strictly as gatekeepers, and strictly trying to dissuade clinical colleagues from utilizing more expensive blood components.

Yet the role, I think, of a transfusion medicine physician, and for all of us who practice this field and for the Food and Drug Administration, is to be patient advocates. That's really our job, and that means to give patients what is the safest and most effective therapy.

Cost is an important issue, but it should not necessarily be our first issue. Patients don't

want to go to physicians who are, first of all, cost effective and, secondly, patient advocates.

Imagine trying -- If you try to tell a patient -- Take a patient who has had chemotherapy for acute leukemia, for example, and is going to require 15 platelet transfusions while recovering from chemotherapy induced bone marrow hypoplasia.

That patient can be exposed to 15 donors, in the case of single donor platelets, or perhaps 90 donors for pooled platelets, six in a pool. Now if you ask the patient, would you mind if I gave you some blood from 75 different individuals, I don't really have to do it, but I'd like to do it to safe some money, what do you think of that -- well, of course, no patient would accept this kind of an approach.

Imagine going to the parents of a newborn child and saying, you know, we have a new way of transfusing this little baby; we're going to expose the baby to many units of blood, but blood is pretty safe and it's going to save the hospital a lot of money. Of course, this is an absurd thing, and no patient would ever accept this kind of an approach.

So the only way that we can accomplish this is by not telling anybody what we're doing, and I don't think it's right.

We've heard from tobacco companies for years, cigarettes do not cause lung cancer, heart disease or emphysema. Nicotine is not addicting. Now what have we heard from the blood banking community?

In 1983, just 16 years ago, we heard that blood transfusion does not transmit AIDS, and if it does, the risk is only one in a million, like any hit and kill by a bolt of lightning. Well, in fact, the risk in large cities in those early years was more like one in 100 to one in 1,000.

The new watchword seems to be blood is safer than ever, and we see it repeated over and over again. Now I don't know. Is this deceptive advertising or what?

Just scanning, for example, a list of topics that were presented at this year's American Association of Blood Banks meeting just a month ago, looking at some of the infectious complications of blood transfusion that were discussed at this meeting, there were discussions about hepatitis B, hepatitis C, HIV and HTLV, because we recognize that we still have not eliminated that risk. It still remains a risk, albeit it smaller.

There were discussions about hepatitis G virus, a virus looking for a disease or for something

bad to do, but clearly transmitted by blood transfusion, and Creutzfeldt Jakob Disease as a potential risk.

There were discussions -- There were abstracts presented on the risk of tick borne infections, human erlichiosis, babesiosis, lyme disease. There were discussions about other parasites like Trypanosoma cruzi, the agent of Chagas Disease, and malaria, clearly agents that we know can be transmitted by blood transfusions.

There were discussions about human herpes viruses. We've been concerned about CMV, but what about oncogenic agents like Epstein Barr virus, human herpes virus 8, also known as Kaposi's sarcoma virus? Are these transmitted by blood transfusion? Probably so, and should we be concerned about that? I don't know. I think maybe so.

Finally, a whole host of bacteria that can contaminate all of our blood components. So just how safe is it?

Well, recently, Philip Morris has come around and said that cigarettes do cause emphysema, heart disease and lung cancer, and that nicotine is addicting. So do you think that maybe it's time for the blood banking community to kind of 'fess up and

admit that we produce a product that saves many lives, but it's inherently risky and, therefore, we should do everything we can to improve the safety of the components that we transfuse, and that this should really be mandatory.

After all, we did think that blood was safer than it ever had been in 1980, and then came AIDS, and we all got killed. So the bottom line here: Leukocyte reduction does cost a lot more, although as you've heard, there are efforts to try and demonstrate that perhaps there are advantages of leukocyte reduction that will reduce costs, but that remains to be seen.

It is definitely achievable. We did it, and I know that it can be done, although I am impressed by some of the difficulties that some of the large institutions have demonstrated that this is not something that can happen overnight for the entire country. But it can be done and, as they say in Washington, it is the right thing to do.

Thank you.

(Applause.)

MS. CIARALDI: Thank you, Dr. Goldfinger.

We will now take -- Dr. Lee, can we still have 20 minutes or should I cut it down? Okay. We

will now take a 20 minute break. Please return to the auditorium at -- It will be ten after three for the open presentations and the panel discussion. Thank you very much.

(Whereupon, the foregoing matter went off the record at 2:50 p.m. and went back on the record at 3:08 p.m.)

DR. LEE: While everyone is trickling back in, we have had a request to make an open presentation, and the order of the process for the rest of the afternoon would be that the open presenter to make his presentation, which should be about 15 minutes, and then after that we will have the panel up at the table, and then start going over some of the questions.

The questions are meant to foster discussion, and other questions can be entertained also.

I'm waiting for the quorum. If everyone would please get back in your seats.

CAPTAIN GUSTAFSON: I have the honor of moderating the fourth and last session of the workshop. When the staff and the audio-visual department heard that I would be moderating this session, they sent a warning: Keep your hands up, and you will not be harmed. I'm not allowed to have any heavy tablets or

touch anything.

Anyway, as Jong mentioned, we do have one speaker who asked to give more than just a couple of words at the microphone. Dr. John Whitbread from Cytometrix, International, in New York will present information on process control for the manufacture of leukoreduced blood components.

Dr. Whitbread, and upon completion then we will invite the panel up for panel discussion.

DR. WHITBREAD: Thank you very much.

I would like to just spend a few minutes during this open presentation session to share a few ideas with you on process control of leukocyte reduced components.

I think the morning session was very interesting in that there seemed to be a new consensus that seemed to be being generated on using some sort of methodology over and above quality control to help us better understand what the process of leukocyte reduction is doing and, moreover, how we can really monitor the process in a comprehensive, reliable way, essentially to make us good manufacturers for those components.

This is a topic which recently was brought up at the BEST committee meeting about a month ago.

The discussion -- Most of the discussion at the BEST meeting was really mostly theoretical and getting into the various questions and various models that one might think about, even in terms of trying to design or implement a statistical process control program.

What I am going to be talking about today is really more the practical side of it: What is process control? How does it compare, really, to quality control programs? And essentially, at the end of the day, how can we use this to achieve our bottom line of being able to accurately predict what fraction of our manufactured component is liable to be outside the acceptable manufacturing range or just flat out fail QC?

To accomplish this, I'd like to break these comments, really, into four points: As I mentioned, to compare and contrast quality control to process control; to talk a little bit about the manufacturing standards one needs to think about in terms of implementing a good process control program; some of the unique technical challenges, and this refers somewhat to the types of models and the types of theory that go into formulating a statistical process control program; and finally, I'd like to finish with some real life experience that we've had with statistical process

control.

Okay. Why process control? Well, we process control essentially to define manufacturing thresholds, traditionally through types of analysis that take, say, a range of values. That would be QC values for leukocyte components -- establish a mean, and then you could sort of imagine the familiar bell shaped curve that gives us sort of a range of what we expect that manufacturing process to produce, and then we might establish sort of standard deviation or confidence intervals outside from that mean that give us some idea of what might be acceptable and what might not be acceptable.

Certainly, traditionally process control has been used in many manufacturing organizations, primarily as, really, a great means of measuring manufacturing efficiency. The pharmaceutical industry, for instance, uses process control, really, for determining and monitoring potency of their manufactured products.

Really, many of the manufacturing industries that are out there use some form of process control to get a better measurement of what the process is doing, rather than solely focusing on the product alone.

Certainly, as a result -- which has been well documented that the implementation of process control helps minimize wasted product and helps increase manufacturing confidence.

Just to quickly go through some of the key differences between product QC and process control: Certainly, from product QC we know that we measure the final product. At the end of the day, what we wind up with is a pass/fail type result. Either we are above or below five times 10^6, and then what we get also with the product QC is, of course, we don't have a clear idea of what the probability may be for future QC failure.

Process control, on the other hand, we're measuring a process. We're measuring the day to day experience of our, in this case, leukocyte reduction process. This essentially gives us a means for measuring a trend and efficiency of the process.

What is particularly attractive about process control is that, by doing this type of measuring, doing this type of analysis, it gives us instant feedback about what our probability of failure and success is as we go forward in the manufacturing process.

Another key aspect to process control is

confidence. We had some talks earlier talking about the sensitivity of QC and process control. Just as sort of a primer to confidence, basically confidence is an indicator based on sample number, frequency and failure rate of the process.

These are essentially what is combined together to give us a confidence of whether or not our process is in or out of control. For instance, we did a quick analysis actually right before this meeting, and if we assume a failure rate of about eight percent -- that is, a leukocyte reduction failure of about eight percent, which is probably very conservative. Certainly, the failure rates that have been reported most recently are quite a bit lower than this, but I think eight percent actually serves us well in terms of this illustration.

What confidence do we have in detecting a failure, using the current QC approach -- that is, of sampling one percent of the product? What you see here is the relative confidence level here and the monthly sample size that you need to detect a failing unit, assuming an eight percent failure rate.

As you can see, with a minimal sampling here of four, our confidence level is really quite low at about 28 percent. Earlier, Dr. Lee had indicated to

us that, really, 95 percent -- as well as other speakers, have indicated 95 percent really being a better number to shoot for in terms of trying to establish a good sense that we understand the manufacturing process.

For this -- Under these assumptions, you would need to test about 35 samples per month to get a confidence level of 95 percent.

Okay. So if we are convinced that process control is the way we want to go, what would we think about in terms of making sort of an idea process control program?

Well, ideally we want it to be interactive. I mean, after all, we have -- everybody has different manufacturing needs, although we're conscious of the five times 10^6. Nevertheless, having a mechanism that allows us to adjust the manufacturing thresholds -- say, if one month we want to try to make a product which is quite a bit better than five times 10^6, for instance -- that allows us to do that.

Certainly, we want to be maximally sensitive to failing process, and perhaps most importantly, provide us a real time state of manufacturing.

Currently, with the sampling of once a

month, this makes it difficult, and perhaps one of the things that we would want to think about in parallel with process control is, if not more samples per month, perhaps more frequently taking whatever number of samples we're going to be taking for that month.

That will certainly help establish getting a closer feel for what the real state of manufacturing is today. After all, we're doing process control to help us get a better handle on the manufacturing process. This type of analysis really becomes important.

Keeping it simple: It doesn't take long for me to stand up here and start talking about statistics, and you start seeing a lot of glazed eyes. I think that one of the key points to implementation of any type of process control program is going to have to be that it ultimately makes it easy for the user to use.

This has got to be something that essentially data can be dropped into and out comes a graphic or out comes a table that gives a real time indication for what that process is doing that week or that day.

Certainly, if we looked into the future and kind of think about what we might want out of sort of

an idealized process control program, it would be certainly to try and be predictive as much as we can be about the future. What is this type of manufacturing trend likely to produce one month or three months or a year down the line?

I think this may be particularly important even for product qualification type analyses, in that we want to try and use this information. Essentially, we're using quality control information. We would essentially use this information and be able to work as much information -- much value out of that information as we can.

So, certainly, one of the things we can do with a lot of these current statistical methods is to help us extrapolate what the future might look like, and I think this is certainly something that we can work towards.

Some of the difficulties -- I'll go through these quick -- in detecting failing processes, since this starts to border on some of this statistical mumbo-jumbo:

Essentially, the current type of distribution that's associated with a leukocyte reduction process may have actually very different types of distributions, and the current methodologies

for trying to estimate probability, at least in a statistical sense, very often tend to underestimate the real probability of getting an accurate estimate of how frequently you're going to have a failing process and ultimately a failing product.

A sensitivity -- The Shewhart method here is considered more or less a standard within the process control circles, but really is probably the least sensitive compared to other statistical methods which I list up there.

Autocorrelation, I'll just pass by. The other key aspect of the leukocyte reduction process that really makes putting together a good statistical program difficult is the very nature of the process itself.

When you consider the range of results that you can get with a QC result, you can be down at the level of sensitivity, which for flow cytometry or PCR may be down to 10^3 leukocytes per unit, are ranging up to 5 million and greater. You can appreciate the large amount of variance that you have within that distribution, and trying to use some of these methods to accurately estimate what your probabilities are becomes very difficult.

Okay. So what are some of the design

characteristics that we would ideally like to put together for a good, comprehensive statistical process control program?

Well, certainly, first and foremost, we want a continuous estimate of the probability defective. After all, without this, process control is useless, and we need to have some way to have this estimate presented to us, if possible, on a daily basis that gives us a very clear idea of what to expect for that day and also be able, again, to maximally use the experience that we have with that process.

The issues of control versus out of control performance criteria: This is, I think, an important issue that in considering a good statistical process control program we think a little about how we want to define these and, certainly, there are some good statistical arguments, which I won't go into here, as to how we might best define control versus out of control.

Similarly, the standards that we define as control and out of control certainly shouldn't occur in a vacuum, and that the standards should be consistent with what medical device manufacturers who have large databases on performance of their products -- that they should be consistent, certainly, within peer.

If one blood service or blood center, series of blood centers has a large collective database, that certainly putting together the criteria for control and out of control performance criteria should be sensitive to that experience.

Lastly, the sensitivity should always be high, and that the level of confidence remains constant. This is sort of a statistical geek point which I think, again, goes along with the point I made earlier about the variance being very large; and when you're working with that type of data, that it becomes very difficult, particularly as the database grows in size, to keep the sensitivity very high while maintaining the confidence at a standard level of, let's say, 95 percent.

So ideally, what might this look like, in sort of a very simple world? Well, we could imagine something like this where, for instance, we have categories here for all units less than certain thresholds.

Again, I mentioned earlier about the interactive thresholds. These are numbers that are sort of important to us from a regulatory level, but perhaps as manufacturers we may have other levels that might be important to us as well.

A target efficiency, that essentially being the probability of producing all of our units under these given thresholds. Then what we might have as what we call measured efficiency. Basically, where are we this week or this month.

Graphically, we could present this as a fairly -- I realize there are a lot of lines on here. It probably looks a little complicated, but essentially this shows a process which is going along here over time, months down here. We have basically production efficiency over here.

Levels for all processes being less than five times 10^6, one times 10^6 and five times 10^5, and by design this particular process is just to illustrate how this might work.

This yellow line, if you follow it along, is showing for the first 100 months or so a process which is always producing units under 5 times 10^6. What we can see is that after about the 109th month here, it now departs from that probability.

What's interesting, and in fact, when you look at real data, real datasets, is that this always seems to bear out. That is that you see sort of a major fluctuation in some of the lower levels prior to getting a defect in your process at your regulatory

level or at your highest level.

So I think this, again, may be the sort of tool that would be helpful, again as manufacturers, to help us get alerted to when processes may be going out of control.

As I mentioned, there's some experience. This is actually from some work that was presented at the most recent AABB meeting and related the experience, actually, in Canada where they used a process control program in 13 blood centers.

Essentially, just to quickly go through the results from this study, was they had six of the 13 centers which were always in control, three of the centers which were in control and then went out of control, and then there were four centers which were, in terms of the statistical process control, always out of control.

This gives you the number of units that were looked at. As you can see, clearly, the failure rate for the ones which were always in control was much better than the ones which were out of control. So, certainly in this scenario, the process control was very beneficial in alerting these centers when processes were going out of control and, clearly, when there was no response to that signal, that in fact they

did get failing product.

So as I just said, the centers received warning ahead of the product QC failure. This prompted retraining of some of the key operations within centers, and they concluded that the process control is a powerful method to prevent increases in the risk of QC failure.

I think this is really an excellent study, and really proof positive of the value of statistical process control when it's applied to a leukocyte reduction process.

So to summarize, the current QC sampling plan, at least as it currently exists, really may not detect substantial numbers of products that are essentially -- that may be failing. Again, this can be improved one of two ways, either by more samples or more frequently sampling.

I tend to think that, in terms of moving towards a process control program, that a more frequent sampling with perhaps some more modest increase in the number of samples would really work out quite well.

The statistical process control provides key manufacturing data, again to make manufacturing decisions. I mean, as manufacturers -- and we want to really have a good feel for what the process is doing

on a day to day basis, that this is a mechanism that allows us to make those key manufacturing decisions.

Process control will augment QC. We're certainly not advocating here that we get rid of QC completely. I think that there's certainly a value to doing the types of QC that's currently being done, and I think that the process control can really be a nice addition to the current QC program.

Certainly, finally, the process control is now a method which evidences accumulating -- Several other studies which were presented at the BEST meeting which related process control experiences using it in the leukocyte reduction process.

I think that as time goes on and the studies accumulate that, again, the message will be that much more convincing.

Just in closing, I'd like to take a quote from the 1987 FDA guidelines on general principles of process validation. With that, thank you very much for your attention.

(Applause.)

CAPTAIN GUSTAFSON: Does anyone have any questions for Dr. Whitbread? Okay. If the panel members, the invited speakers, would come to the panel, and Dr. Jong Lee will briefly go through the -- recap

the workshop objectives, and then we will open the floor to discuss Dr. Lee's key questions, key elements, whatever, and also any other issues that were raised during the presentations or any other questions that any of you may have.

CHAIRMAN LEE: I guess we've lost two members of the panel from the original plan. That creates some additional space at the table, I think. If Dr. Whitbread is interested in joining us, he would be welcome.

I'd like to simply go through some of the points that I made earlier this morning, as takeoff points for discussion. That is not to say that discussion should be limited to these questions, but I think what we'll do is have each question up on the slide while we are going on, and try to step through them at approximately at a pace of eight minutes per decision, trying to leave some time for any additional topics that might arise at the end of the day.

Once again to remind you that participants, while we are discussing things, may refer to the following aspects, but not to dwell on them as primary topics, and we've gone over this extensively today: Cost, clinical risk and benefits and scientific principles -- we have heard a lot about them. They

should be mentioned as they relate to implementation issues.

The first point that I made this morning was: Should FDA recommend specific implementation criteria applicable to all blood establishments or should FDA provide only the framework within which blood establishments adopt an implementation plan specific to each center?

Key decision number 2: Should FDA recommend a simple transition period of 12 months or briefer or should FDA support transition periods that are longer than 12 months which may allow further maturation of cost, clinical and scientific issues?

Decision number 3: Should the current FDA guidance on leukocyte reduction be retained for use during the transition period or should the definition and QC of leukoreduction be updated from the current FDA recommendations for implementation during the transition period?

Number 4: Should blood centers, if eligible to participate in the CBER pilot program for streamlining licensure, be able to obtain the license for leukocyte reduced blood products by the simple self-certification process, referring back to the existing leukocyte reduction standards, or should blood

centers, if eligible and interested, continue to be required to submit evidence of compliance with existing leukoreduction standards for CBER review in obtaining the license to ship leukocyte reduced blood products across state lines?

Lastly, if a blood center already licensed for whole blood, red cells and platelets may self-certify in supplementing its license to include leukocyte reduction, should it be able to self-certify compliance with the existing 1996 FDA memorandum on leukocyte reduction or should CBER write a new pilot guidance for leukocyte reduction under GGP in order to allow self-certification, although the pilot guidance may not be substantively different from the existing 1996 memorandum?

I guess the last question is really referring to the speed of the GGP process. We all realize that regulations take a long time to formulate, but guidance -- although guidances are much quicker, they, too, take some time in terms of making a statement.

So having gone over these, I'll go back to decision number 1 and leave this up throughout the discussion, and then we'll move on to the next decision and so on.

The floor is now open for comments, questions, regarding this topic. If there are no particular views, I guess we could do a vote or something, but I don't want to do that.

DR. BIANCO: Oh, there are views.

CHAIRMAN LEE: Thank you.

DR. BIANCO: I think that during the discussion several speakers -- You saw that there are different approaches, different ways to get there. I think that the most successful guidances and regulations that came out of FDA were when they set a goal that everybody should attain but didn't really try to micro manage the institutions to get to that goal.

I wish you would continue following this path. I think it is very important that we define what is the goal that is -- what we are going to call a leukoreduced product, and that's the subject of some discussion; and second, obviously, when we are going to get to this point.

Here, the framework -- I love frameworks.

CHAIRMAN LEE: Are there any opposing views? Just to confirm, I also thank everyone in the audience who has persisted through the day to come to the panel session. I realize the panel discussions necessarily come at the end of the workshops, but in

fact are the most important part of them, and I thank you for staying with us.

Just to confirm my impression of the opinions of those still in attendance, if I could simply see a raise of hand for those in favor of the former, that specific implementation criteria be reserved to each blood center to formulate on their own.

All those that are in favor of the bottom sentence, could I see a raise of hand, please? Looking around, that seems to be the majority.

All those in favor of the top? That makes it black and white and explains the lack of comments as an opposition to Dr. Bianco's statement.

In that case, we'll move right along. I think this might be more contentious. We've heard opposing views built right into the presentations today. Should FDA recommend a simple transition period of 12 months or briefer or should FDA support transition periods that are longer than 12 months which allow further maturation of costs, clinical and scientific issues?

Would anyone like to make some statements about that? Ms. Norrell?

MS. NORRELL: Well, Well, based on our

experience, it is a complicated conversion process, and there are infrastructure changes that need to happen in many of the facilities. So I don't think it's feasible, really, for many centers to do anything briefer than 12 months unless they were initially set up to do that.

If there is some flexibility to be built in even greater than 12 months, but not much more, but we've definitely needed a full 12 month period to go that route.

CHAIRMAN LEE: Dr. Snyder.

DR. SNYDER: Yes. I think certainly longer than 12 months, but I would like to see an upper limit as well. I think, left to its own devices, the medical -- some parts of the medical community would let it go on ad infinitum. So I'd like to see some by a certain period of time as well, but certainly longer than 12 months.

CAPTAIN GUSTAFSON: Dr. Snyder, from the presentations today did you get a feel for maybe what might be a maximum time period?

DR. SNYDER: I heard three years most frequently, but others may have heard something else.

CAPTAIN GUSTAFSON: I mean, you heard three years, but you heard from the presentations like where

Red Cross is, where BSI is, where ABC is. Did you get an idea that perhaps three years might be an outlier, that maybe a shorter time is realistic?

DR. SNYDER: Well, the impression I got is that the Red Cross and other major blood services, blood suppliers, would certainly be compliant in much closer to 12 months, but I'm concerned about the ten, 15 percent of Mom and Pop groups or places that may not be able to comply quite that readily.

So I'm sensitive to that, but some people have other administrative opinions about that. But I think most people will be closer to 12 months, but I don't know whether, therefore, you should make it 12 for everybody.

CHAIRMAN LEE: Yes? Would you please state your name and affiliation and proceed with the question or comment?

MS. SAZAMA: Yes. My name is Kathleen Sazama, and I don't know what my affiliation is at the moment.

Let me just raise the question that's related to this, and I know you're trying to avoid the clinical and scientific issues, but in fact you can't. The implementation period that permits the collectors to ramp up and actually provide the components is only

one part of this equation.

I'm troubled still that the right players are not present for a discussion about how the implementation then occurs in the actual delivery system, which is to patients in hospitals.

So I think the statement as written is a little simplistic, if I may say that, and shouldn't be decided in the absence of thorough discussion with respect to the impact of this process at the other end. We know lessons have been learned from implementing testing, for example, that did not adequately address how inventory transfers occurred, and harm happened to patients.

So I think it's premature to answer this question completely unless you were to modify it to say, you know, how long will it take for the collection side to be prepared to provide these components, and then convene the right group of people to discuss how long then would it take for the receipt of those components and the transition of the policies and practices in hospitals to accommodate the new components, and what is the plan?

If you're going to transition, what inventory should be being managed in hospitals in the transition? Is it what the collectors can provide or

is it what the collective wisdom of those who care for patients decide is the right thing for patient care?

So I just would like to have the record reflect that I believe the question does not adequately address the implications of a decision on this point.

CHAIRMAN LEE: Yes, thank you for your comments. Although these questions are formulated by CBER, I'd like for the responses to come as much from the audience as well as from the panel rather than people from the agency responding.

Are there any counter-comments or any other comments?

MS. NORRELL: I would just like to add one more statement, that another critical part of the decision is whether we'll have enough filters. So we can't really set a date without knowing that we're going to have the materials that we need to be able to implement.

So that's an important piece of information that I don't know.

DR. GOLDFINGER: If I could respond, I don't see the problem in implementing this at the hospital level. The big problem at the hospital level is simply the cost that's involved.

If the blood centers can deliver leukocyte

reduced components, then we can transfuse them. The analogy to -- I'm not sure if you were alluding to the problem associated with NAT testing, because the problem with that has been that the suppliers have not been able to deliver the kind of turn-around time that allows us to transfuse only NAT tested blood.

I think that is a problem, but I think with leukocyte reduction, if the suppliers could provide it, then we could transfuse it.

MS. SAZAMA: I think that that oversimplifies the problem, Dennis, if I may say so, and I ask your indulgence to let me speak again.

There are current practices in many hospitals in which bedside filtration is a common practice, for example. In planning a transition, you want to avoid that. There's no need to have duplication of those activities, as just one simplistic idea here.

The second is that there is a moment in time when you go from what you had to what you will have. How long is that moment in time, and how much advance planning needs to go into it?

Yes, it is true that the budgetary implications are a part of this, but I don't want to lose the fact that there is process and policy and a

lot of institutions in which the clinicians believe, rightly or wrongly, that they still are in charge of the therapies to their patients.

I don't disagree with your position that we should assist them in doing what is good for patients, but that takes time to lay the foundation, for the medical staff to understand what's going to happen and why, for administration to make the adjustments to what they expect in terms of how their resources are going to be deployed, and then the physical act itself of simply swapping out or using up or whatever it is that we're going to do.

I mean, if today our region -- I'll use Philadelphia as an example -- were to say to us, tomorrow you can have all the leukoreduced blood components to transfuse, if that were theoretically possible, there still would be implications inside the walls of the blood bank and the transfusion activities that have to be planned for.

So those are the kinds of things that I was interested in addressing. So there are policy, process, and procedure activities in hospitals for which there will be implications. Just like the diversity of opinion we've heard here today, I bet you not everybody agrees with what you said, and not

everybody agrees with what I'm saying.

It takes time to make those transitions. That's all I'm saying, and a plan for implementation should not simply look at how soon can we have the material to deliver. It's also how soon can we put in place the right process to make sure that delivery happens the way it's intended.

DR. GOLDFINGER: I would agree with you, but I thought that -- That's why I think that the three-year approach is a reasonable one. I think that you would be right. If it would be done in less than a year, that might be asking too much.

In addition, I think that a couple of the speakers making this mandate to the FDA that they somehow work with HCFA to get better reimbursement is one of the most important things that I heard here today. It's got to be done.

It's not possible for one agency just to turn their back on the other and just say that we don't see it, and we really don't want to see it. It's a serious problem that, I think, could be changed, because there's some logic involved here. I mean, this is something that's good for our patients.

CHAIRMAN LEE: Could you come to the microphone?

MR. DICKSTEIN; I'm sorry to go out of order, but I'd like to answer Ms. Norrell and Dr. Goldfinger's comment. I'm Rob Dickstein from Pall Corporation.

Speaking for Pall, we're prepared to meet the filter demand of 100 percent leukocyte reduction by August of 2000, in answer to your question, Stephanie.

CHAIRMAN LEE: Thank you.

DR. PITTMAN: Yes. I'm Dr. David Pittman. I'm representing the Barnes Jewish Christian group out of St. Louis, Missouri. We transfused about 67,000 red cell units last year, and we certainly support a longer time such as three years to allow the implementation of this.

We have hospitals doing all different sorts of leukodepletion, from almost none to almost everything. I especially enjoyed seeing Dr. Lee's written comments regarding the BPAC members' opinion that quotes, "There's insufficient scientific evidence to conclude that the effect of leukocyte reduction is clinically important for the typical transfusion recipient."

We believe it's important to have a longer time. We still believe that prospective, randomized, controlled trials are necessary, not only to answer the

scientific issue but to aid, as Dr. Goldfinger said, getting HHS or HCFA and FDA together as far as having some type of reimbursement.

We see that very important, because we're setting, as all hospitals are, in a fixed reimbursement, and it's hard enough when you're certain that something is scientifically valid to decide if you're going to get this laser or if you're going to get some other technology. But you're asking us to take something where many of us as transfusion professionals still believe there's not adequate scientific evidence to use it in 100 percent of patients, and what are we going to give up?

Are we going to have fewer nurses? Are we going to have less SOPs, less adequate QC, fewer OR techs, fewer custodians; because in our system what gets cut in general is personnel, the people that actually take care of patients.

We don't think that that's appropriate to institute something like this without given time to prove this.

I understand Dr. Snyder's opinion, that though there may not be a single reason that justifies universal leukoreduction, that perhaps the cumulative effect of many less than complete indications might

help.

As I came in, I noticed a homeless man on Wisconsin Avenue. If you would each take a dollar bill out of your pocket and tear the right third off, I'll collect them and take that to that man; but he still won't be able to buy a hamburger and a cup of coffee.

So I kind of -- I understand what Dr. Snyder is saying, but it often doesn't work out, that many small things add up.

Many of us are not resisting new developments. We're not doing that at all. We're attempting not to accept the wrong new developments, and the FDA should take that advice.

In doing that, you might look, as you told me a year ago that you would put more transfusion professionals, that transfusion medicine is part of their life, day to day, hour to hour and minute to minute, rather than so many researchers, epidemiologists, people that do a little bit of transfusion, on the BPAC. That may benefit you as well.

(Applause.)

CHAIRMAN LEE: Thanks for your comments. If you could, move to this microphone over here.

MR. MURPHY: I'm Scott Murphy from

Philadelphia. I'm very sympathetic with the last comments, and we have many customers in Philadelphia who agree with you.

I think the other side of the coin of the way this is being structured, waiting for three years, is that a blood center can ramp up to make the products available, but if there's a three-year implementation period, it may encourage hospitals that have a difficulty with this to wait.

So that it will be hard for a blood center to ramp up to 100 percent, for example, in a year or a year and a half, if the full implementation of the program won't take place for two or three years.

I think what Kathleen was saying is that the hospitals have to be in step with what we're doing, and from many different points of view.

CHAIRMAN LEE: Dr. Sayers?

DR. SAYERS: Merlin Sayers, Carter Blood Care, Bedford, Texas.

There's one other maturation that I suspect is going to take longer than a year for us to fully appreciate, and that has to do with how universal leukoreduction is going to influence our inventories and the management of those inventories. If we look at donor deferral these days, it's tantamount

to 5,000 cuts. What we're looking at here are another two cuts which we must not underestimate.

One has to do with how many donors will we be deferring through no reason other than filter failure, and then how many donors are we going to be losing for reasons that have already been referred to, namely, the incidence of sickle sell trait in African American donors. That group has already been highlighted as a group of individuals who are very important in their contribution to the national inventory.

We certainly are going to need more than 12 months to decide how to manage what is going to be an obligatory additional deferral rate superimposed on already compromised national blood supplies.

CHAIRMAN LEE: What time -- Could you stay up there just one second longer, Dr. Sayers. Do you have a time frame in mind or just simply longer than 12 months?

DR. SAYERS: Well, we didn't hear anything about other people's experience with exactly what filter failure rates are, and our own experience with knowing what the loss of individuals with sickle cell trait is, is an experience which is too small for me to rely on to confidently predict how much longer we're

going to need, but I strongly suspect it's going to be longer than 12 months.

DR. HEATON: I would certainly like to comment from the blood center's perspective. The practical reality of manufacturing is that you can run two inventories up to about 30 or 40 percent, but once you cross 50 percent, you can't run two inventories; because you cannot allow hospitals to order leukodepleted as a boutique product when half of what you're manufacturing is leukodepleted and half isn't.

So as a purely practical manufacturing matter, once you cross the 50 percent barrier, you have to mandate universal leukodepletion on your customers.

If you link that to your stated goal, that you believe that universal leukodepletion is medically appropriate, I think you're going to need an implementation period probably of around two years, because it takes about six months to get organized. It takes about six months to drive the first piece of your transition, and probably a year to wrap it up. But I can tell you that anyone who gets over 50 percent will be desperate to switch the rest of their production into leukodepletion, simply as a practical matter of meeting the order of the customer who wants leukodepleted.

MS. NORRELL: And that has been our experience as well.

DR. MENITOVE: Yes, and ours as well. On the other hand, I think we have seen, at least in our area, the hospitals that are willing to switch. They have come forward and have said we're going to 100 percent leukocyte reduction. In our area, it's approaching 40 percent of usage.

I don't see or hear that the other hospitals are willing at this point to make a commitment. So at least from the area where I'm from, we could persist in this chimeric 50/50 relationship probably for the indefinite future or at least three years.

My only thought is, is that period of time long enough, Jong, to do some of those things that you were talking about before in terms of an ethical and time period long enough to put together some studies.

On the other hand, I'm not exactly sure what we're looking for. If we're looking for reduction of post-op infections, I think we could get an answer potentially, or at least another answer, to that question. But of some of the other open questions, I'm not sure a study could be designed and implemented and completed in that period of time.

CHAIRMAN LEE: Dr. Snyder.

DR. SNYDER: You know, not all hospitals are the same. At our institution we have four blood bank directors. I spend all of my time focused on this issue, and I have a certain amount of sway with the institution, small though it may be.

So if I push for leukoreduction -- the concept, if you don't know your jewels, know your jeweler -- the administration will rely on what I say, so far, as being a reasonable approach. They think I'm a reasonable person.

Many hospitals, the blood bank director is off doing autopsies, surgicals, hardly ever is in the blood bank. To say that they're not willing to leukoreduce and convert isn't because the blood bank director doesn't feel that it's appropriate.

He or she just isn't pushing the issue, and the institution will say, well, I'm not going to give you another penny, and he says fine, and he or she goes and finishes the autopsy and lets the blood bank run on its own.

So I don't think it's appropriate to say that a couple of centers are really interested in this, but the vast majority of hospitals don't want to, as if they've studied the issue, they've had debates and

they've talked about it.

It's really, I think, apples and applesauce or apples and alligators, and maybe looking at -- it would be worthwhile to take a survey of academic institutions where there are similar people focused on blood banking all the time and other hospitals where they're not, and seeing what those statistics show.

MR. DRESSLER: I'm Kent Dressler with the Park Madison Clinical Labs in New York City, and New York Biologics.

I think that I would agree, of course, with the latter part of this statement, that there is a need for longer than 12 month period, but I think that the FDA has to continue to maintain the active role that they took in driving this process through BPAC to get this movement towards the universal leukocyte reduction occurring by supporting actively in ways that they need to figure out how to do, to have the studies that can be done right now to look at cost effectiveness and clinical effectiveness.

There is a transition period occurring where there are both products being used, and it is a data acquisition maneuver that could be done now that will disappear as an opportunity once the universal leukocyte reduction has been achieved by whatever

process, sterile docking or in-line.

So I think that there has to be a continued active involvement on the part of the FDA to get data collected that currently is collectable, and to make that a process that they work out somehow with HCFA so that everybody can be brought into selling this, which is inherently probably a good thing, to the community that ultimately has to pay for it.

CHAIRMAN LEE: Thank you. Dr. Holmberg.

DR. HOLMBERG: Jerry Holmberg with the Joint Readiness -- or Joint Clinical Readiness Advisory Board with Military.

I was one of the -- I think that was my last BPAC that we voted on that. As a former member of BPAC, I strongly encourage the longer than 12 months, primarily for the fact that it gives some time for scientific issues to be resolved and questions to be answered.

I also raise the issue of the cost. I agree. I don't think we have everybody sitting at the table today. We talk about HCFA, the reimbursement costs, what's best for the patient, but also what if the patient can't afford it, who picks up the tab on that, the cost centers involved with the leukoreduction.

So I think that 12 months -- We need to have longer than 12 months. Also I raise another issue, that you know, three years may be too long. However, I think Captain Gustafson mentioned this earlier in her presentation, about the real estate on the label and the issue with ISBT.

We've been down this road before with ISBT and the label, and one of the problems was that nobody set a definitive date. The only date that was definitive was when the Red Cross said they could not do it until this certain date, and that happened to be, I think, December 31st of 2001.

I think that there's an ideal opportune time to maybe correlate and orchestrate some of the dates together. One of the things that we can learn from Canada is how do we go through the labeling process as this country goes through a period of time of transitioning to a new labeling process where the product code will be a mechanism that hospitals can capture that reimbursement cost, that I think it might be wise to maybe put on the outside limit when do we think that we will be converting over to the ISBT-128.

I also agree with Captain Gustafson as far as the real estate on the label and what do we mean, and Dr. Bianco with his comment about the FFP and do we

put leukoreduced fresh frozen plasma.

I think it's absolutely ridiculous to have that on the label. However, I strongly would encourage that, if we are going to go to 100 percent universal leukodepletion, that what we do is we put that into the circular of information, that the premise says that we are starting with a leukoreduced product, so that we're not messing up our label.

I guess my encouragement to the FDA would be to bring more people to the table to iron out some of these issues as far as the cost, the transition, along with ISBT, and also, most importantly, to give us enough time to be able to answer some of those scientific questions.

DR. BIANCO: I want to add a couple of words to what Jerry just very emphatically told us. We may not be able to time everything together, as it appears that we will go to universal leukoreduction.

There are technical issues, and there are the donor issues related to them. That is, to leukoreduce red cells seems to be a reasonably straightforward matter, provided that you choose either the in-line or the docking system, with all the other issues that we discussed. But the platelet issue, I think, is very concerning, at least to me.

If we made a conversion today to single donor platelets, I don't know how long it's going to take us to ramp up to be there and to have practical means of doing pooled platelets leukoreduced. I don't think we have them. I think that our techs in the components lab today, they would get entangled in the number of wires and tubing that would be there, and we would have deaths in the lab.

So probably red cell -- probably, again, when this is written, we will have to say that our goal is that we'll get there, but we may not get there with all things at the same time.

CHAIRMAN LEE: Any other comments?

MS. NORRELL: I just want to clarify what that last recommendation was. Are you suggesting that we set or that the FDA would set a timeline specific to red cells first, period, and the other would fall in behind?

CHAIRMAN LEE: Interesting approach.

DR. GOLDFINGER: Well, it's interesting, but you know, probably one of the great advantages of going to an all leukocyte reduced inventory will be the elimination of pooled platelet concentrates, which is a common sense approach that is not coming from academic medical centers but rather I find that the pathologists

running a blood bank at a small institution is very happy to make those kinds of changes, especially if they're mandated so that he doesn't have to be looked upon by his administration as doing something that is unnecessarily increasing the cost.

I must say, I've always been a great fan of the Red Cross, but I've never really looked upon the Red Cross as the great leader in transfusion medicine, but it's interesting how things have come around; because the Red Cross is pushing this issue tremendously, and I think rightfully so, the efforts toward safer plasma coming again from some blood centers as well as the Red Cross.

I think that these are good things for the country.

DR. BIANCO: I want to hear Dr. Snyder, about the pooled platelets.

DR. HEATON: Well, I would like to comment on our pooled platelets. Dennis, you're referring to a 30-year-old product. The reality is that there is in-line filters, leukodepleted platelet, random donor platelets available now, which would meet most of the criteria that you're concerned about, avoidance of cytokines and other cellular products.

In addition, in Europe it's standard

practice to pool buffy coats and make platelet products out of four pooled buffy coats. Again, it's a very cost effective system. It's one that's worked extremely well in practice, and the only reason it's not available in this country is a very restrictive approach toward the licensure of pooling and a very restrictive approach toward the licensing of the use of a sterile docker.

So I think that there is great life in random donor platelets, and I think that we should adjust our regulations to be more sympathetic, to allow the licensure of the very low cost, high quality product.

DR. BIANCO: Do you know any center that is licensed for the preparation of buffy coat derived platelets in this country, and how long do you think -- and what would we have to do to do that?

DR. HEATON: There is none licensed, and the licensing cycle would be at least 24 months.

DR. GOLDFINGER: Just one point. You know, my issue on single donor platelets really has nothing to do with leukocyte reduction. It's strictly donor exposure, which to me is such a basic issue.

I can't imagine anyone, any patient that you could find that wasn't -- that hadn't lost his

faculties that would choose pooled platelets over single donor platelets, especially multiple transfusions, 50 extra exposures. It's just so unbelievable to me to think that anyone would do it, and in fact, nobody in his right mind would do it.

It's only if we choose not to ask and to make this the only product available.

AUDIENCE PARTICIPANT: But, Dennis, no one would choose a non-leukoreduced blood product.

DR. HEATON: I don't think leukocyte reduction -- that's more of a blood banker's thing. I must say, I don't think leukocyte reduction is something that the public would jump on the way they would these multiple exposures. It's not just an extra person. It's like so many more people to whom you have to be exposed.

If you're in a hospital setting and you see patients who have to be transfused, they're so frightened. A physician who sticks himself with a patient's blood or a donor room nurse who sticks herself or himself runs down to the employee health or something for some careful monitoring and maybe a shot of gamma globulin. That's one exposure, and it's not 50. I guess I don't understand it.

CHAIRMAN LEE: Go ahead.

AUDIENCE PARTICIPANT: I just wonder, does any of the panel want to comment on whether three years is too long, which was what I was implying or is everybody happy with that?

DR. SNYDER: Well, I discussed it with the homeless person out there, and we both agree that two years would be -- I'm concerned about the inventory issue. That's something that was brought up, and I think our Red Cross provides us -- and we've had discussions with them, and I think two years -- If we decided not to go to leukoreduction or if we did and the rest of the state didn't, and had to keep dual inventories, it would be almost an impossible situation.

So I think that should be something that really needs to be considered. There are efficiencies on the blood center side as well as on the hospital side that have to be considered.

You know, I mean, HCFA -- I believe the basis of this is HCFA believes that we're over-bedded in the United States, and they would like to see X number of hospitals closed. How we do it is up to us, and I don't know how it's going to happen.

In Greenwich Hospital, for example, in Connecticut, it's a relatively small hospital with

maybe 150 beds. Do you think that the town of Greenwich is not going to want their local hospital to remain open? I mean, they have the money in Greenwich to be able to raise millions of dollars in a very, very short period of time.

I think that's the problem we face, that we're looking at a mandate to close hospitals with a group of individuals that don't want to close the hospitals, and we're stuck with advances in technology, and I don't think there are simple solutions to this.

So I'm not really sure how the quandary works out, but economics, I think, on the blood center and the hospital side has to be considered in the equation.

CHAIRMAN LEE: In the interest of moving forward, if you could keep your comments kind of brief. Go ahead.

DR. PITTMAN: It's interesting that Dr. Snyder discussed that with that homeless person, because when I gave him five dollars, it was obvious he was mute.

I agree with Dr. Goldfinger. I'm one of the people that has not used random platelets since 1992 in my institution for the donor exposure problem. Am I the only one that worries, however, about if we

make a flat statement saying that random platelets are no more, that we're going to take so many donors out of our red cell donations unless the regulations are changed, because they will now become platelet pheresis donors who are very faithful and give, you know, as often as they can. I worry about that. I don't know if anybody has studied that.

DR. HEATON: Well, that's the issue that I was attempting to address. As we go to universal leukodepletion, as a matter of manufacturing convenience we will want in-line filtration.

In-line filtration means no random donor platelets. No random donor platelets means more pheresis. More pheresis cuts into red cells, which means multi-component pheresis, and that then means changes to the way we regulate the pheresis segment of our business in order to maximize production.

So there is a technological knock on effect of this type of decision. To respond to Dr. Lee, I think the manufacturers' main concern is that there be a sunset. If it's 22 months or 26 months or 28 months, I really don't care, but I don't think it should be longer than three years, and there should be a sunset.

One way of handling that would be to withdraw a licensure of non-leukodepleted products and

state the time period of sunset, and three years, I believe, will be quite adequate. We could probably do it in less than that.

CHAIRMAN LEE: Dr. Sazama.

DR. SAZAMA: Just one other point that has not been mentioned specifically, and that is there are many hospitals, particularly the smaller hospitals, where inventories are not kept on site, and the ability to get single donor platelets in a timely way that benefits patient care is an issue.

In fact, even getting the ones that Dennis doesn't care for, which is a pool -- and just a parenthetic comment -- the majority of the platelets that are transfused among the eight hospitals I have previously been associated with are not to support heme-onc patients with multiple transfusions.

In fact, they go to people who get one or two dose of a pool of four. So the relative exposure is much less. You have to keep in mind that there are many places where a pool of random is better than no platelets at all.

So I think the availability part of this, which was alluded to on the donor side, but is also -- you know, as a practical matter, some platelets are better than no platelets, and even though they may not

be the exposure that you would prefer for yourself, there are many places where you got to have something, and even the availability of pooled randoms is not that easily acquired.

So you start building in time delays where patients are in need of transfusion, and there's nothing for them. I think that cannot be ignored.

CHAIRMAN LEE: Thank you. Dr. Klein.

DR. KLEIN: Harvey Klein, Clinical Center, NIH.

Three years seems like a very long period, to me. I don't see how I could explain to the American public that their mandate through BPAC, if you believe that that is their mandate, came, and it took our organizations three years to implement this. I don't think that that's rationale, if we think this is a better blood component and we're accepting that.

I agree that hospitals should be part of this equation, because there certainly are issues that have not been addressed today that are important for hospitals, and they need to be addressed.

It also seems to me that, hearing what I've heard today about the major blood collectors in the United States, knowing what I know about the European blood collectors, we can do it well with all due haste,

and we can do it sooner.

There doesn't seem to be any reason that, if we reevaluate halfway through a period and find that, in fact, my optimistic views have been totally wrong, that we can't say, you know, maybe we should go an additional six months.

AUDIENCE PARTICIPANT: Just one question. Why are you rejecting the -- for both red cells and platelets? I mean, the filter is manufactured and, in fact, other countries are using it. I know it produces some technical problems, and it's not easy to work with, but it is not a slam-dunk that you can't make leukoreduced platelets.

So I'm just wondering, is it just felt to be impractical, too expensive, too difficult to write the SOPs, all those things?

DR. HEATON: Yes, time to license, and it's also quite a tricky filter to use. So you've got to be careful with the manufacturing process. That's quite a demanding filter. Terumo has one, I believe, and Asahi has one as well.

CHAIRMAN LEE: I'd just like to make one last comment before we move forward to the next question.

The American Hospital Association was

actually invited as speakers -- as presenters for this workshop, to which they could not accommodate. If there is any member representation at this time from American Hospital Association, referring back to Dr. Sazama's comments, I would welcome that. But if there are none, we'll go forward.

Okay. I think we have gone over that fairly thoroughly. The next issue -- Are people interested in a show of hands or something? Yes? I have to defer this to Captain Gustafson. Should we go through that for each one of these?

DR. GUSTAFSON: Well, I think we're kind of running out of time, if we do a vote for every one. I think we have got guidance. I mean, I think we've heard people in terms of that 12 months is not enough time, and I think we have to work from there.

CHAIRMAN LEE: Okay. If we have time, maybe we'll come back to that at the end of the day.

Moving forward then: Should the current FDA guidance on leukocyte reduction be retained for use during the transition period or should the definition and QC of leukocyte reduction be updated from the current FDA recommendations for implementation during the transition period, which is obviously going to be somewhere between one and three years, as the way it's

shaping up right now?

Any comments from the panel?

DR. HEATON: Definitely. There are several areas of the guideline that I believe need urgent attention, the first of which is we need to define prestorage leukocyte depletion. That is not defined in the guidelines. It's absolutely critical.

We have different products with different manufacturers' instructions, with different filtration periods, and we don't have defined -- We don't have a product definition. So I think that's a critical step.

The second step is the quality control process, the QC process. The four or one percent was fine for a boutique product where you weren't making much of it, but the reality is you're asking an entire system to switch, and any manufacturer would tell you that they use statistical process control in order to control the quality of their products.

The BEST committee of ISBT recently had a whole half-day seminar just on statistical process control as applied to leukocyte QC. I know the FDA has experts on that topic, because it's a very common manufacturing issue. I would seek that the QC segment be amended as well.

I believe those are two critical elements

that should be changed.

CHAIRMAN LEE: Yes, Dr. Menitove?

DR. MENITOVE: I think this might be a nice opportunity for the professional associations that we all belong to and the FDA to work together. It may be less cumbersome for the professional associations to come out with some recommendations first that may tide it over until whatever that interval is, at which time then the FDA guidance could come out.

DR. HOLMBERG: Jerry Holmberg. I agree with Dr. Heaton. There's just one more parameter that I'd like you to look at in that QC package, and that's the 85 percent red cell recovery.

Coming from an institution that freezes a lot of red cells, what do you do when you de-gloss those red cells? Are you going to go from the 80 percent to the 85 percent or just how do you handle those other kind of manipulations?

DR. HEATON: I would also like to add the comment that I attended yesterday the Donor Suitability Workshop, and linked to this I believe it would be very important to amend the guidelines relative to pheresis, particular red cell pheresis and platelet pheresis.

I know that you're reviewing those regulations, but an implication of universal

leukodepletion will be much more pheresis, and the implication of more pheresis means multi-component pheresis, and I believe that we need, in parallel with amending the leukodepletion guidelines, to amend the pheresis guidelines to allow multi-component pheresis and indeed more frequent platelet pheresis during the year.

CHAIRMAN LEE: Okay. If there are no more comments, I would like to move forward.

Issue number 4 -- This is regarding the pilot: Should blood centers, if eligible to participate in the CBER pilot program for streamlining licensure, be able to obtain license for leukocyte reduced blood products by simple certification or not?

DR. BIANCO: Yes.

DR. HEATON: Yes. Me, too. I would comment. I was talking to Captain Gustafson, I think, some four years ago to discuss what we believe to be a critical issue here, and that is at the moment the FDA treats the change in the manufacturing process as an individual unit change requiring approval and sometimes proof of manufacture.

The reality is the manufacturers develop a product. They usually develop a pretty specific SOP, and they go through a very good quality licensing

process. I would seek that the FDA should require the manufacturers' detailed manufacturer's instructions, a specific validation protocol, adequate that an end user or a purchaser could acquire that product, perform the validation according to the manufacturer's SOP, determine that their manufacture complied with the manufacturer's reference standard, and proceed without proof of purchase.

I think that would reduce the workload on the FDA. It would transfer the responsibility for adequate instructions to the manufacturer, where it should appropriately be, and it should transfer responsibility for effective and appropriate operation to the user of the system, which is also where it should be, and then the RA can inspect and just people against the predefined standards.

I think this would be a huge step forward for the blood banking industry.

CHAIRMAN LEE: I see. Since the last issue is so closely related to the fourth, I might as well just consider them together.

If a blood center already licensed for red cells, whole blood and platelets may self-certify, then should the existing 1996 memorandum on leukocyte reduction be able to serve that purpose or should CBER

write a new pilot guidance document to that extent?

I think we just heard a comment in direct response to that problem from Dr. Heaton.

Any other comments? From the floor, yes?

MS. GREGORY: You might know I couldn't pass up this opportunity. Kay Gregory from the American Association of Blood Banks, and also the Coalition for Blood Safety.

This idea of self-certification is something that we've been trying to work with FDA for a number of years now, and it seems to me it's time to finally move forward instead of just talking about it.

MR. DRESSLER: Kent Dressler. Just one comment. I know it's embedded in the law, but it certainly is something silly about shipping materials across state lines and having anything to do with protecting the public or patients. That really doesn't make any sense in terms of licensure issues.

CHAIRMAN LEE: Thank you. Since we seem to have a few minutes still in the panel discussion time, I would simply go back to 2 and actually have a brief show of hands -- I'll try to step through this rapidly.

It's clear that it's got to be somewhere between one and three years, is sort of what I hear. So those that persist to the last minute get the most

say in shaping FDA's thinking.

I'll start at the upper limit. For those who are in favor of three, could I see a brief show of hands, please? For those who are in favor of three years as the maximum upper ceiling of time limit, could I see a show of hands, please?

Okay. How about two years?

Anything between two years and one year?

Thank you very much.

I think we are right on schedule, and I would like to thank Dr. Harvey Klein for accepting the difficult charge of being the spokesperson for today's workshop. Dr. Klein will have the last words, at least for this workshop today and, obviously, he needs no introduction.

DR. KLEIN: Thank you very much. It's a pleasure to be here.

The task that I was given was to summarize this day's workshop, but not necessarily to summarize each speaker's talk, and I don't plan to do so, nor do I even plan to try to summarize all of the data that's been presented. It's really too long, and it's really unnecessary. In fact, since this is being transcribed, I'm sure you'll be able to read it very soon on the 'Net.

So what I'd like to do is try to encapsulate the nucleus of the discussion of the day, and give some editorial comments along with it. Those will be my own. They won't belong to the FDA, and they certainly don't represent the National Institutes of Health.

We've been reminded that leukocyte reduction has been front and center formally for a very long time. There was a workshop already held by the FDA in March of 1995, and the Blood Products Advisory Committee discussed the issue regarding cytomegalovirus in September of '97.

Then there was what I think we can only characterize as an overwhelmingly positive response of the advisory committee in September of '98, 13/4, none against and three abstentions. Now one can argue that the advisory committee is constituted of the wrong people or you can argue a variety of things, but if in fact that represents the advice to the FDA, I think it is overwhelming.

That is, positive benefit to risk ratio, and based on the available science, and excluding the well meaning, if somewhat overemphasized potential risk of Creutzfeldt Jakob Disease and new variant Creutzfeldt Jakob Disease, the data do not support

blood transmission of those agents; and even the murine studies don't suggest that depletion of leukocytes would make the blood supply safer.

We're reminded that the FDA's own mandate is safety and efficacy, not cost, but cost may be a safety factor if inappropriate expenditures prevent more appropriate public health interventions. So cost has clearly been on the FDA's radar screen, and it should be. We've heard that over and over and over today. But cost shouldn't be the decisive factor in public health.

This meeting wasn't designed to review the science and the indications, except as background, but was designed for implementation issues. We may, in fact, be a little late in this arena, since nine countries are already involved in universal leukocyte reduction, either doing it or are well into the implementation phase.

They have taken between nine months and two years to get to that phase. However, the United States has six times as much blood collected each year as the country with the largest amount of blood.

So I think we can be excused if universal implementation of leukocyte reduction is not necessarily quick in this country and is not

necessarily easy. But we can and we must benefit form the experience of those other countries.

Prior to universal leukocyte reduction, we know that the U.S. already is leukocyte reducing about a quarter of its blood, and is going to go to about 50 percent, by our estimates, by the year 2000.

About six percent per month is what I heard, and about 70 percent of what is done is prestorage, and prestorage needs to be defined.

The manufacturers, to no one's surprise -- this is going to really be tough -- they've recognized these trends and the international trends, and they've accelerated their production already, both with filters and with apheresis strategies, and they are prepared for universal leukocyte reduction, at least at the six percent per month increment, and I suspect a good deal more, despite Y2K concerns. However, they've reminded us today that they don't take the primary responsibility for licensure review -- that belongs to CBER -- for logistics, for reimbursement, but they're willing to help the industry in all of those areas.

They've already asked CBER to consider expedited licensure review and an end result guideline, not a detailed type of process guideline, in their guidance document, and to help with HCFA reimbursement,

which again, we've heard, might be a critical issue.

We've heard from the two review units of CBER, the Blood and Plasma Branch, Division of Blood Applications, Division of Hematology, the laboratory of cellular hematology. I bet not everyone knew that two different units of the FDA dealt with leukocyte reduction.

It was certainly good to hear them both speaking today in public and giving us an opportunity to both hear their views and to criticize them and for them to hear one another.

There seems to be, fortunately, a consensus thinking here. First of all, recognition that different centers, hospitals and manufacturers do differ in their mission, in their size, and in their operational complexity.

The FDA guidance looks like it will let manufacturers come up with a plan in six months and an implementation in somewhere between two and three years perhaps, and most interestingly, to change the default in human blood collected in the United States from leukocyte containing to leukocyte reduced.

I like that term, Jong. I don't know whether that was yours or not, but I think changing the default is perhaps precisely what we want to do. As a

physician who, in the early seventies and late sixties prescribed digitalis leaf -- it was a brown substance in a jar that was spooned out to patients -- I don't think that would be acceptable today. It's simply not pure enough, and I think we need to increasingly think of our blood components in the same way.

The proposal by the FDA seems reasonable. It's a better product. Many organizations seem to be on target for one to two years. So let's get on with it, with all appropriate speed.

Three years seems to be a little long, to me. Three years have been suggested, because they would allow clinical trials for controversial indications. I have several reservations about that.

As someone who's done clinical trials for their life's work, I sincerely doubt that they are going to be done or going to be done well or going to be done completely or definitively in a three-year period of time.

I think, if some were to be done, they would be of scientific interest, but they won't really affect the public health, because leukocyte reduction is going to be done anyway, and whether some of these controversial indications turnout to be important or not important will become a moot point for public

health purposes.

There are several other advantages of stretching out this implementation period: certainly, as a cushion for reimbursement, we heard, and concerns about blood availability. But I hope that we can, in fact, move more expeditiously, and the United States system of collection and provision of blood has been able to do so in the past.

We had discussions about the standard, five times 10^6 leukocytes per unit, fewer than such, which differs in the U.S. than in Europe, as well as the quality control requirements. Much has already been written about process control and testing.

As was already said, half of the BEST committee's meeting this year dealt with that. The FDA ought to look at these issues. They know about process control.

Quite a bit has been published, both in this industry and in others, but they should make their requirements the simplest consistent with safety and efficacy, perhaps a 95 percent confidence, that 95 percent of the components meet whatever standard is defined.

Do we need to revise the current guidelines? Listening to the two units, I guess the

answer is yes and no. The leukocyte reduction guidance, relatively new, has to be somehow revised. The platelet pheresis guidance is clearly going to be revised. The answer is probably yes, but the optimal timing for such revisions remains to be seen.

We heard about requirements for licensure, and we hope and assume that the FDA will have the resources to process these expeditiously. If the public says something is safe and effective, then the public ought to give the FDA the resources to provide mechanisms for licensure.

We appreciate the issues of labeling with the new default, and we appreciate the need for process control, and that all leukocyte reduction will be done in current good manufacturing process fashion, according to regulations, in appropriate laboratories.

That probably ends the era of bedside filtration, which in terms of safety and efficacy, that's probably a good thing.

There are still major logistical issues. Some deal with cost, single donor platelets, sterile docking, in-line filters, source leukocyte availability, sickle trait blood, loss of units of blood in the filtration process. These are all going to be worked out.

There are some helpful, specific recommendations to the agency. Some say they should mandate change. This might help make it a little bit more palatable to the hospitals which are under the financial gun, but perhaps there are other ways of getting a standard of care other than a regulatory agency's mandate.

They need to relook at quality control issues and strategies and process control, and they need to help with HCFA in reimbursement, because the issue, after all, is reimbursement. It really isn't cost.

I must admit that, looking at the implementation plans of the Red Cross, Blood Systems, Incorporated, and others, I'm impressed at the ability of our heterogeneous system of blood collection and delivery to respond to such a sea change with such rapidity, especially when there's a public mandate.

We still have to deal with our customers. I've heard that over and over again today, but our customers aren't just the hospitals, and that's coming from someone who runs a hospital transfusion service. Our customers really are those who receive the units of blood, and we need to bear that in mind.

Do our customers see universal leukocyte

reduction as a better component? Do we need a mandate? Are there threats of litigation? Who defines this as a new standard of care? How do we deal with the costs? I think those are all issues that remain to be addressed.

We heard, I believe, that any guidance that's issued by the FDA will be in a draft format for public comment, and I think that, too, is a good thing.

We also heard, I believe, that guidances and regulations differ, and that guidance isn't binding unless it's associated with other regulations such as with cGMP. Don't believe it.

If there is guidance issued for universal leukocyte reduction, I suspect you'll do it, and I'll do it. Otherwise, that yellow tape may appear across our door. But more importantly, that guidance is important for public health and for public confidence.

I found the workshop today incredibly helpful. It's told me where we are, and I think it tells me where we're going. I suspect that universal leukocyte reduction may be done well before the final guidance is published.

That, in fact, would be a father in the cap of the stewards of the American blood supply.

Thank you.

(Applause.)

CAPTAIN GUSTAFSON: Thank you, Dr. Klein. That was a wonderful summary. I think you hit all of the salient points, and we're very pleased with that.

I would like to thank all of you who stayed until the bitter end. It's too bad that we don't have workshop incentives to give out, out in the lobby. Maybe next time. But we thank you so much.

We appreciate your input, and I think we've had a very valuable session.

(Whereupon, the foregoing matter went off the record at 4:42 p.m.)