DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE SIXTY-SIXTH MEETING

VOLUME II

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9:00 a.m.

Holiday Inn 8777
Georgia Avenue
Silver Spring, Maryland

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

F. Blaine Hollinger, M.D., Chairman

Linda Smallwood, Ph.D., Executive Secretary

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Mary E. Chamberland, M.D.
G. Michael Fitzpatrick, Ph.D.
Richard J. Kagan. M.D.
Marion A. Koerper, M.D.
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Gail Macik, M.D. Mark A.
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Paul J. Schmidt, M.D.

NON-VOTING REPRESENTATIVES:

Katherine R. Knowles, Consumer Representative
Toby L. Simon, M.D., Industry Representative

TEMPORARY VOTING MEMBERS:

Paul R. McCurdy, M.D.
Kenrad E. Nelson, M.D. Carmelita U. Tuazon, M.D.

C O N T E N T S

P R O C E E D I N G S

MS. SMALLWOOD: Good morning, and welcome to the second day of the 66th meeting of the Blood Products Advisory Committee.

I am Linda Smallwood, the Executive Secretary.

On yesterday, I read the conflict of interest statement that pertains to this meeting. I do have that statement available if anyone would like to view it, however, those things that were read on yesterday pertain to today's session with respect to conflict of interest, and if there are any declarations to be made regarding the topics to be discussed today, please do so at this time.

May I ask that, if you are using a cell phone, that you would turn it off, preferable, or have it on low ring so that it will not interfere with the proceedings here.

If there are no declarations, then I will turn the meeting over to the Chairperson of our Blood Products Advisory Committee, Dr. Blaine Hollinger. Thank you.

Committee Updates

DR. HOLLINGER: Thank you, Linda.

We have some most interesting Committee updates on some topics that are of real interest to this group, and the first one is an update on a requirement for syphilis testing. And Dr. Ruta is going to give us the background

information.

By the way, after each one of these, there are some public hearings--I mean, people who want to speak to these issues, so rather than go through the three updates and then have the issue discussed, we'll have the individuals comments, if they would, afterwards.

Dr. Ruta?

Update on Requirement of Syphilis Testing

DR. RUTA: Good morning, Dr. Hollinger. Thank you. Good morning, everyone.

10:05 I wanted to give a brief update on where we are with some of the regulations that we published--last year's committees--where, and the public's aware.

On August 19th of last year the FDA published, in the Federal Register, two proposed regulations.

If I could have the overhead, it just has the title of the one under discussion now. It's "Requirements for Testing Human Blood Donors for Evidence of Infection Due to Communicable Disease Agents."

Now, this proposed regulation would extend the current testing requirements for HIV and hepatitis B, which are currently in the regs, to include requirements for testing for hepatitis C and for HLV 1 and 2. And it also proposed to require supplemental testing whenever a donation tested repeatedly reactive, or for one--by one of the

screening tests for the required infectious disease agent; and, in addition, a proposed requirement that donors testing repeatedly reactive would be deferred as donors.

Now, we also published a companion rule, is a notification rule, that would require that donors who are deferred would then be notified that they were deferred and told why they were deferred.

And we initially had a 90-day comment period.This was extended for another 30 days to allow for oral presentation of comments at a public meeting. And, first, I wanted to thank everyone who sent in comments. We appreciate that. We received a total of 23 letters to the testing regulation, with multiple--you know, with comments included, and those were submitted to the docket.

Okay--now, specifically, within this reg, we asked about the continued--or, this rule, we raised the question about the continued utility of testing for syphilis. And as the committee's aware, the syphilis test was first introduced in 1938. Early on in the AIDS era, it was also though to have value as a marker of high-risk behavior. And the question of continued syphilis testing has come up periodically. In January--last time was January '95, in which an NIH Consensus Development Conference concluded--and I'm quoting here--"Because the contribution of serological tests for syphilis in preventing transfusions in admitted

syphilis is not understood, the panel concludes that testing of donors for syphilis should continue."

So, as part of our rule-making effort, FDA solicited comments, along with data, on the value of donor-testing for syphilis as a marker of high-risk behavior, as a surrogate test for other infectious diseases, and in preventing the transmission of syphilis through blood transfusion.

We received a total of seven letters containing comments; five of the comments supported eliminating syphilis testing, and two of the letters opposed eliminating syphilis testing. We received some data on the subject, and the ARC was kind enough to provide some data, which they also presented at the public meeting in November, and it's contained in the docket. And their data was of a preliminary study which indicated that the DNA for T. pallidum could not be detected in serologic-positive samples, as with the STS positive as well as FTA-positive--antibody-positive samples, and the conclusion is that--their conclusion is that therefore the treponemas were not likely to be circulating. And they used PCR methods on a total of about a hundred samples. But because the sample size was small the ARC has proposed conducting a larger study.

In addition, the CDC has been reviewing national

surveillance data to learn more about cases of early syphilis identified through attempted blood bank donations, and the CDC is also conducting laboratory studies to assess detection of the T. Pallidum DNA from persons with varying stages of infection and reactivity by the traditional RPR and microhemoglutination assays.

We are considering bringing the issue syphilis testing to the BPAC in September meeting if the data is ready for presentation.

That's all I had to say on the subject.

Questions?

DR. HOLLINGER: Any questions of Dr. Ruta?

Yes--Dr. Ohene-Frempong?

DR. OHENE-FREMPONG: Yes, with regard to high-risk behavior, what's the current epidemiology of syphilis in the U.S.?

DR. RUTA: Can I ask--well, I'll answer part of the question, then I might see if Mary or someone from CDC wants to address that.

With regard to high-risk behavior, that question was addressed, in part, in the '95 Consensus Conference, and the issue, more specifically, was raised about the role of syphilis as a surrogate for HIV, and the panel concluded that, in the face of the specific HIV test, that there wasn't a value to syphilis testing.

The ARC also presented--or I guess it's the Rudd Study also presented a limited amount of data suggesting that the syphilis testing also did not have value for other--only had value for--let's see--I'll just read what they said, so it will be more accurate here--that "the STS positive donors have a--"--excuse me--it's their conclusion that "--the probable risk associated with STS-positive donors is largely due to STS-related risk factors. And when STS-related risk factors are not considered, STS has no significant value as a surrogate indicator of behavioral risk."

The actual data is contained within the docket, which is publicly available.

I don't know if Mary or someone from CDC or NIH wants to add to that.

DR. CHAMBERLAND: I think the only think that I'll add is that the Division of STD Elimination is really putting forward a push to try and eliminate syphilis from the United States. There has been a concern that has been brewing for the last year or two of a resurgence of syphilis--clusters of syphilis cases--that have been seen in places like Los Angeles, and Florida and Seattle-King County. And these cases have been occurring in these areas in--among men who have sex with men. And I think we heard yesterday concerns that this may reflect--ahh--sort of a

return to risky behaviors, or new populations of young adolescents--young men--who have not been part of the earlier HIV epidemic. And so there is concern in that arena, and a push to try and move towards prevention. But it would clearly be a challenge.

If the issue is presented at the September BPAC, CDC will have representatives from our Division to speak to the epidemiology, as well as some of the data that may be pertinent to the question about syphilis screening of blood donations.

DR. HOLLINGER: Dr. McCurdy?

DR. McCURDY: This is just a comment. The NHLBI co-sponsored with OMAR, the Consensus Conference that was cited a few minutes ago, and one of the major questions--although it was not specifically stated--was once you start doing a test on blood donations, can you ever stop? And the answer thus far has been "no." So I'm very curious to see what happens if we go further on this.

DR. HOLLINGER: We may do that yet.

Any other questions? Yes, Dr. Epstein?

DR. EPSTEIN: I just wanted to add a comment.

CDC has published an MWUR, in which it is described that the donor screening for syphilis is one of the best existing mechanisms for picking up early cases. And it brings to light the question of to what extent should

we practicing public health in the donor room?

In this country, we don't actually use the donation process as a primary instrument of public health screening --you know, for example, cholesterol screens, you know, ESAs, genetic tests for a variety of inborn metabolic disorders, etcetera. And I think that perhaps one of the dimensions of the question, when we finally bring it to the fore: if we're able to dismiss the issue of syphilis screening to protect the blood product with respect either to syphilis or, you know, co-incident risks, we'll still be left with the question of are we wiling to drop it, recognizing its public health utility?

And that opens the door to a whole new dialogue about what are we doing when someone walks into the donor room? Again, in this country, we don't see it primarily as a opportunity to practice public health, but there are many countries where, in fact, they do.

DR. HOLLINGER: Then it also raises the issue of who should reimburse that, as well, if that's the issue going to be dealt with.

Yes--Dr. Simon?

DR. SIMON: I think it's interesting, because I believe in the plasma donor centers it was instituted historically as a matter of public health, since plasma derivatives cannot transmit. We do the syphilis test every

four--initially, in every four months, and I think that it was instituted primarily for that reason--as a public health screen and donor issue. So I think that's an interesting historical vignette, that there is a precedent, I believe, if I'm correct, and it will be interesting to see how that plays out.

In other words, we don't do syphilis testing on the donated unit. We do it on the donor every four months.

DR. HOLLINGER: Dr. Schmidt?

DR. SCHMIDT: Just a comment that I don't think the public health is a function of the FDA, and we get into an awful lot of things if we adopt that attitude.

DR. HOLLINGER: If there are no other questions, I do know that there are--there is one group, the AABB,that has a statement that they would like to present, and I'll have them do that, and then we can ask further questions at this time.

Yes--Dr. Katz?

DR. KATZ: Does anybody at the table not know who AABB is?

[Laughter.]

DR. KATZ: I'll skip the first paragraph.

We thank the committee for this opportunity to comment.

The serologic test for syphilis has been retained

in the U.S. for two ends: prevention of transfusion transmitted syphilis, and as a surrogate for risk behaviors associated with HIV infection.

Transfusion-transmitted syphilis has not be recognized in the United States for more than 30 years. And, in fact, in 1985 an FDA committee recommended eliminating STS for blood donors. This recommendation was not implemented when the issue of the STS's value as an HIV surrogate was raised.

The reasons for the disappearance of transfusion syphilis are multiple, including the declining incidence of infectious syphilis in this country and donor deferral policies' reducing the presentation of those at risk for infectious syphilis. Storage of red blood cells at refrigerator temperature is probably an important contributing factor as well. Still, there is transfusion of fresh red cell components--albeit rare--and platelets are stored at room temperature.

Receipt of antimicrobial therapy by those ill enough to require transfusion support may also be important in preventing either infection or recognition of transfusion syphilis. From a biological standpoint, it must be emphasized the spirochetemia associated with transfusion transmissibility to T. pallidum generally occurs before the STS is reactive.

At the NIH Consensus Conference in January '95 that's been referred to a couple of times, it was concluded--and I quote--:current blood storage conditions would not appear to provide an adequate margin of safety against transfusion-transmitted syphilis. Should the donor screening test be eliminated. Further information concerning T. pallidum survival under blood and platelet storage conditions, and the application of molecular techniques to assess the presence of T. pallidum DNA in serologically positive units, would allow better assessment of this question."

Data presented at the AABB Annual Meeting in the fall of 1999 addressed this recommendation. Orton, et al., tested platelets from 82 PK-TP positive, FTA-ABS confirmed donors using two PCR methods, and found none with detectable DNA.

Regarding the value of the STS as a surrogate for other transfusion-transmissible diseases, even prior to the implementation of sensitive NAT assays for HIV and HCV, the Consensus Development Conference concluded--and I quote--"Cross-sectional studies and examination of prior donations from donors undergoing HIV seroconversion indicate that serologic tests for syphilis have very little value as a surrogate marker for HIV infection in recently infected persons who have not yet developed detectable antibodies to

HIV. Syphilis testing is likely to identify less than one such donor annually within the United States. This low efficacy of syphilis testing as a surrogate marker of HIV is not sufficient by itself to warrant its application to all blood donors. Low positive predictive values for HBV, HCV, or HTLV infections similarly do not support retention of syphilis testing as a surrogate for these infections."

Ramsey and Sherman reviewed FDA-reported blood component recalls in the United States from 1990 through '97. Of an estimated 241,800 components recalled, 57 percent--or 137,000, were for incorrect syphilis testing. These were primarily in a single large recall of units where weakly reactive STS results might have been called negative. This recall was classified by FDA as a class III recall--quote--"not likely to cause adverse health consequences."

With these points in mind, AABB supports the elimination by FDA of the requirement for performing an STS on each whole blood donation.

DR. HOLLINGER: Louie, before you leave--and I also want to ask Dr. Simon about this--could you tell us what the--give us some numbers of donors that are eliminated each year? First-time donors and repeat donors that have positive tests, that are removed from the donor screening--in the blood banking industry and then the plasma

industry, as well?

DR. KATZ: In my center, we turn up between 100 and 120 reactive RPRs a year, less than 5 percent of which confirm with FTA. Those--the components from those donations are generally lost, because of the time-frame involved in completing confirmatory testing. The donors are not deferred if their FTA is negative. But, as I said, of 100 to 120, less than five a year at my center, out of 55,000 donations confirm.

And I can't give you accurate first-time versus repeat, but most of ours are repeat donors. As a matter of fact, we have probably 25 or 30 donors, I believe, who have repeatedly reactive STS on repeated donations, and we're able to salvage their red cells, but not their platelets.

DR. HOLLINGER: Is Dr. Stramer here? Can she tell me--from the American Red Cross standpoint? And then I'd like to ask Toby?

DR. STRAMER: For Red Cross donations, I just have percentages, and we collect 6.2 million. So one just needs a calculator to convert.

Our reactive rate for FTA is .18 percent. And of those--of the total, then, .08 percent--or about half of the FTA positives--are also RPR-reactive. So our algorithm includes a total treponemal confirmatory test by florescent-antibody test, and that was the reactive rate of

.18 percent, and then we take the FTA reactives and test them by RPR.

And, again, of those--of the total donations, .08 percent are RPR-reactive.

Sharon Orton from the Holland Laboratory is also here, and can add a little bit more about the characteristics of donors who are FTA and RPR-positive. So I would suggest that we let her make a comment as well.

DR. HOLLINGER: If I look at these numbers, from what you just said, that's about, then, 62,000--correct me if somebody has also done this--but it looks like about 62,000 that are then reactive with the RPR. And these were deferred, is that correct?

DR. STRAMER: Correct.

DR. HOLLINGER: Okay. And they haven't been tested for DNA or anything like this at the present time.

DR. STRAMER: Well, just the subset that was described by Dr. Ruta and Dr. Katz.

DR. HOLLINGER: Okay.

Yes?

DR. RUTA: So, I'm a little--I have a question, if you don't mind. I'm a little confused, because I'm looking at the data, and the data that you guys gave us said there were 1.8 million donations between May '93 and September '95. Of those, 2,151 were STS reactive, and 1,274--0.7

percent--were confirmed by FTA. And then you go on to say that you have 6 million donations annual, 7,200 lost components, and 4,200 temporarily deferred donors.

I was wondering how you get a number of 60,000?

DR. STRAMER: Well, I believe the percentages on the data--okay, well then they do--

[Pause.]

DR. HOLLINGER: It looks like, from mine, it's 12,400 and 6,200, then--approximately. Yes.

Dr. Nelson:

DR. NELSON: The public health benefit was mentioned, given that despite the loss of donors the screening might detect some infected cases or people who don't otherwise know they're infected.

Are there any data on how many of these .1 percent or so already know that they're--are already aware, and how many are really--have public health significance; are new cases, unknown cases?

DR. ORTON: Yes, I'm Sharon Orton, from the Red Cross, that has done the work the infectivity. I've also done a case-control study of blood donors who are PK-TP-positive, and both FTA-positive and FTA-negative. And in that case-control, 50 percent of individuals who do have a confirmed positive FTA do report a previous history of syphilis, and knew that they had a previous history.

And, interestingly, there was also about 40 percent of individuals who have a negative FTA who report having a previous history with positive screening tests in the past. So even the serology is not consistent over time.

DR. HOLLINGER: Thank you.

This is really just an update here, but it gives us some idea of what we're going to be discussing, probably, in the future.

Louie, do you have another question--comment?

DR. KATZ: Well, the numbers from Red Cross and my center sound a little difference, which is because they screen with a confirmatory test--PK-TP--and we screen with the RPR, which is substantially less specific, I think, than the PK-TP.

DR. HOLLINGER: Thank you.

Colonel Fitzpatrick?

COL. FITZPATRICK: The DOD rate for RPR is about .03 percent--0.3 percent--for the screening. And I don't have the confirmatory. And those are mostly first-time donors.

But our confirmatories are very low. I'll see if I can--I think I have those.

DR. HOLLINGER: Okay. Thanks.

Yes--Gail?

DR. MACIK: I wanted to get--with these positive

tests, but there has not been a documented transmission? Is that what I heard when you started off--in 30 years?

DR. HOLLINGER: Well, documented transmission but, of course, it's tested--I mean, one would argue it's tested for syphilis. So--

Louie, do you want to comment on that? You made the statement.

DR. KATZ: I actually didn't say "documented." I said "recognized"--number one. And I think that's a legit issue, and gave some reasons.

In the 15 years I've been doing STS, 50,000 times a year, and I also happen to run the STD clinic in our local health department, and we've not picked up an early syphilis through that testing in 15 years. And it's only early syphilis. Often, prior to seroconversion, in fact, where spirochetemia that would be transmissible by transfusion occurs.

DR. HOLLINGER: Dr. Schmidt?

DR. SCHMIDT: I reported that last case in the United States, and I can bring the picture next time. It was a florid, secondary syphilis, with multiple skin problems. So it became very obvious, very soon.

DR. HOLLINGER: Thank you.

Thank you, Dr. Ruta. I think--oh--

DR. RUTA: If you don't mind, I had one more

update.

DR. HOLLINGER: Yes. Yes.

Regulation of HIV Drug Resistance Tests

DR. RUTA: Thanks. It looks like there's a lot of interest in the syphilis question, and thank you for your comments.

There's one more update that I wanted to give, and that is on regulation of HIV drug-resistance tests, and the committee remembers that we brought this for discussion in September, and we've been getting a number of letters on the subject, and so I just wanted to make a statement, both for the Committee and for any interested public, as to what our current thoughts are on the subject.

As of now, we have not yet approved any tests, but as the Committee knows, drug resistance--HIV drug resistance tests are tests that detect mutations in the HIV virus and may be useful in monitoring infected patients and in their treatment. And such tests may be provided in several different formats, and those would included as an intact finished tests manufactured by a company that's then shipped to a laboratory for use; two, it can be presented as an anilide-specific reagent--that is, a company would make primers or probes, and that they would be shipped to a laboratory for use at the clinical laboratory; or, three, it can be provided as an in-house test by the clinical

laboratory, using only in-house developed reagents, and the primers and probes. And as the Committee is aware, if a manufacturer makes a--or produces a finished HIV drug resistance test that's shipped to a laboratory for use, they are required to obtain FDA approval. And last September we brought the issue of approval of drug resistance tests to the BPAC for discussion, and the Committee voted that they thought such tests could be re-classified from Class III to Class II.

I wanted to talk a little bit about the other two categories, because we've been getting some questions about it.

So, as I mentioned, the HIV drug resistance tests can be performed using in-house developed tests. And FDA believes that ASRs--anilide-specific reagents, or primers and probes, using tests intended for post-diagnosis monitoring and treatment of patients infected with HIV, including ASRs using HIV drug resistance assays, fall within the definition of a Class III device that's described in the ASR regulation in our regulation. And just for purposes of anyone who wants to know, the cite of the regulation is 21 C.F.R. 864.4020. And manufacturers of ASRs would be required to obtain FDA approval.

A clinical laboratory that develops an in-house test using an anilide-specific reagent that is in commercial

distribution is required to append the following statement to their test result--and I'm going to quote now. This is also in the regulations--but I'm quoting: "This test was developed and its performance characteristics determined by--"--and you fill in the laboratory name--"It has not been cleared or approved by the U.S. Food and Drug Administration."

And moving on to the third category in which we're talking about in-house tests using in-house developed reagents: "The FDA also believes that clinical that develop in-house tests are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the Federal Food, Drug and Cosmetic Act. Currently CBER is exercising its enforcement discretion in electing not to require pre-market approval for in-house tests developed by a clinical laboratory for its exclusive use in the monitoring of HIV, provided that claims made by the clinical laboratory are only for the analytical capability of the test. Clinical laboratories are advised to provide only the actual results of analytical sensitivity testing conducted on samples, and no clinical or medical claims about the benefit of making treatment decisions on the basis of these tests should be promoted, suggested or claimed.

"The FDA encourages clinical laboratories that have developed the reagents for in-house use to append the

statement--"--and, again, it's the same statement that I read before, I'll just read it again--and I'm quoting--"This test was developed and its performance characteristics determined by--"--fill in the laboratory name--"It has not been cleared or approved by the U.S. Food and Drug Administration." --end quote--"--to the test results."

I also wanted to let people know that while we are not, at this point, requiring submission of applications from clinical laboratories that develop their in-house tests for HIV drug resistance, we are--will accept submissions on a voluntary--if they're submitted on a voluntary basis for such HIV drug resistance tests.

Thank you.

DR. HOLLINGER: Any questions in regards to this issue?

I know there's a lot of interest in both genotypic and phenotypic testing for drug use and so on, and so I think this is going to be an important issue to do--to regulate in some regard, down the line anyway.

No other? Okay, thank you, Dr. Ruta.

The next update is on the risk of HCV to sexual partners, and--Dr. Biswas.

Risk of HCV to Sexual Partners

DR. BISWAS: At the December 1997 Blood Products Advisory Committee, the issue of whether or not sexual

partners of persons who test positive for antibody to hepatitis C virus--anti-HCV--should be deferred was addressed. At that meeting, scientists from NIH, CDC and the Harvard School of Public Health presented data from studies of anti-HCV-negative spouses or sexual partners of individuals with anti-HCV. The data indicated that transmission of hepatitis C virus between spouses and sexual partners appears not to be a problem.

Under current procedures, at the discretion of blood establishments' medical directors, prospective donors who are sexual partners of anti-HCV-positive individuals may donate blood, provided that their partner does not have a history of clinically apparent viral hepatitis during the year prior to donation.

A somewhat different approach has been taken with regard to donors of tissues for transplantation. The July 29, 1997, FDA Guidance for Industry document entitled "Screening and Testing of Donors of Human Tissue Intended for Transplantation" states that persons who have had sex in the preceding 12 months with any person suspected of having hepatitis C infection should not be accepted as a tissue donor. FDA will be reconsidering the policy of tissue transplantation.

FDA is maintaining an awareness of results of further studies that are designed to evaluate sexual

transmission of HCV. While sexual transmission of HCV, such events appear to be rare. For this reason, history of HCV-positive sexual partner is not a strong correlate of HCV risk in a donor.

DR. HOLLINGER: Thanks, Robin.

I think I'll have the--I think, again, Dr. Katz has a comment. Where did Louie go?

Any comments? Oh.

Yes, Dr. Simon.

DR. SIMON: I think it's worth making the panel and the representative of the agency aware that in the plasma industry, the comment practice is defer sexual partners because of the global harmonization issues. And most of the fractionators insist that we defer these individuals. Scientifically and medically, I agree with the agency and find this a troublesome practice. It also, I think, gets into issues of privacy and so forth, when we start intruding into people's sexual histories.

So it is a very hot issue, and if it were possible to come to conclusive scientific conclusions here and to seek harmonization internationally on this issue it would be very beneficial to the plasma industry.

DR. HOLLINGER: Thank you.

Yes--now, Dr. Katz.

DR. KATZ: Thank you for your patience while I

practice medicine.

The AABB opposes addition of deferral of whole-blood donors as a consequence of sexual contact with HCV-infected partners. Data from CDC and multiple other published sources suggest that the prevalence of infection in the steady sexual partners of HCV-infected people is at approximately the population background. Although persons with multiple sexual partners may be at increased risk, it remains controversial whether this represents sexual transmission or un admitted and unrecognized parenteral exposures. Because the infection is uncommon, if not absent, among the steady sexual partners of HCV-positive persons, the CDC does not recommend that HCV-positive persons with a steady sexual partner need to change their sexual practices; nor is it recommended that such partners be routinely tested.

If the risk is low enough that neither barrier precautions nor routine testing is the standard of care, it would seem illogical to recommend that such partners be excluded as donors. As a result of the above considerations, the FDA to date has not required donor deferral for sexual contact with HCV-infected persons. There is even less reason to consider such deferral at this time because the implementation of NAT testing has reduced an already low risk of HCV transmission by blood transfusion to

virtual zero.

Thus, the AABB feels that donor deferral based on contact--sexual contact--with an HCV-positive individual is inappropriate and a wasteful use of limited donor resources.

Thank you.

DR. HOLLINGER: Thank you.

Any other comments from the public on this issue? And how about comments from the committee? Or questions?

I'll just share with you, if I could, the little bit of data that we've done, because we've had an interest in this issue about sexual transmission. We've looked at about 400--over 450 couples that--in which the index case had hepatitis C. And of those, all but four--all but four--admitted to a potential parenteral risk factor. So only four didn't admit to one potential risk factor that was parenteral.

5:00 In this group there were 30 couples--approximately 30 couples that were both positive; in which both partners were positive. We've looked at 18 of these--or 19 of these, so far--for--by single-stranded confirmation polymorphism evaluations to see how close they were to each of the individuals. Nine of these, or 10 of these had different genotypes. So, clearly, they didn't get it from each other.

OF the remainder, only one was sufficiently close to each other to suggest that they might have acquired it

from that individual. And when discussing that with that individual--they'd been married 20 years, I think since 1982, and this was about 1998--they'd been married about 18 or 20 years, and the woman had shared needles only with her husband during that period of time. So it's been our contention most of the time--I think Dr. Nelson and their group has had lots of experience with the issue also--that it's very unlikely, or very uncommon for sexual transmission to occur from one partner to the other. You can never really exclude it. If you assume that they're getting it from the parenteral source, then you never can really say, well, they might have also gotten it from a sexual transmission. So, I mean, that's--you have to sort of take that into account. But it must be very uncommon.

Now, I believe--I think there probably is a difference in acute disease, where there is very high concentrations of RS in the window period, with very little antibodies and other things, and I think that may be part of the difference that we've seen with the comments that have come from the CDC initially, where they were looking at acute transmission, and felt that there was some transmission going on at that time. But outside of that source, I think it's very uncommon, at least in our experience.

Yes--Dr. Nelson?

DR. NELSON: I think, you know one issue that--the biology of HIV is pretty well known, in terms of receptors, and where the receptors are. And receptors for hepatitis C, actually a couple, have just been identified. And it's not clear--I mean, it doesn't make logical sense as to why hepatitis B and HIV should be readily sexually transmitted. And this debate was--you know, early on, the feeling was that HIV was only transmitted by male-to-male sex, and it's obvious now that that's not the primary transmission worldwide.

But I think that, you know, a lot more needs to been done on the biology of infection with hepatitis C. It's conceivable that its related to receptors in the genital tract or something like that, and I think that, you know, more needs to be done on this.

But I think that, really, all studies have shown it's rare. The real question is, you know, is it absent? And I don't think it's absent. Because, you know, if it requires a blood-to-blood transmission, that can occur with sexual transmission, as well. So there's a lot we don't know about the biology of hepatitis C transmission.

DR. HOLLINGER: I would agree with that. It's probably not zero, and that's what we tell our patients.

Any other comments?

Okay. Thank you, Robin.

Colonel Fitzpatrick?

COL. FITZPATRICK: I just need to go back and correct those figures, since it went into the record.

For 1996, the deferral rate in DOD for FTA positive donors was .039 percent, which equates to about 429 donors. In '97, it was .037 percent, which is about 407 donors, and in '98 it dropped to .023 percent--about 250 donors.

DR. HOLLINGER: Thank you for that correction. It's on the issue of syphilis.

Okay. Thank you, Robin.

The final update is on the relative sensitivity of HBsAG and HBV NAT tests. And, again Dr. Biswas.

Relative Sensitivity of HBsAG and HBV NAT Tests

DR. BISWAS: Data presented at the March 16, 2000 Blood Products Advisory Committee meeting indicated that hepatitis B virus nucleic acid testing--HBV NAT--of source plasma donations using the format of testing mini-pools containing 512 donations currently being performed under IND, might offer little improvement in sensitivity compared to hepatitis B surface antigen--HBsAG testing--of individual donations, using some of the more sensitive HBsAG tests. In regard to this, FDA is organizing studies in collaboration with NIH, NHLBI, that directly compare: one, HBsAG testing of individual samples using various HB-AG screening assays

to, two, HBV NAT testing using the 512 sample mini-pool format for testing source plasma.

At the present time, whole blood and components for transfusion in the United States are not tested by HBV NAT assays. HBV NAT testing of all blood donations has been implemented in Japan and is being discussed in Europe. FDA is also reviewing the lower limits of detection of all currently licensed HBsAG tests and their various incubation times, tests that are used to screen the blood supply. After completion of this review, FDA will decide whether to change the lot-release requirements of licensed HBsAG tests in regard to lower limits of detection.

We welcome the submission of any existing data on high-sensitivity tests for HBsAG. The data should contain sufficient details so that meaningful head-to-head comparisons between tests can be made. And, in fact, we're beginning to receive such data.

DR. HOLLINGER: Thank you, Robin.

There are two people who have asked to speak to this issue. Again, the AABB, Dr. Louie Katz, and then followed by the American Red Cross.

Open Public Hearing

DR. KATZ: The review of the relative sensitivity of approved and pending hepatitis B surface antigen assays versus HBV NAT by FDA is timely, as U.S. blood collection

facilities are being asked to instituted mini-pool NAT screening for HBV by European plasma fractionators within the next year. Major U.S. blood banking organizations are resisting this request, based on a combination of cost-benefit considerations and the general, but not universal, benignity of HBV infections acquired by transfusion.

The European fractionators are being asked to consider the use, instead of NAT testing in mini-pools, of more sensitive HBsAG assays, detecting less than .1 nanograms per mil of antigen, that are pending FDA consideration and approval. In addition, some U.S. suppliers of recovered plasma to the European market have proposed the exclusive use, when a donor is found to be antechoir-positive of anti S-reactive units, and perhaps HBV NAT when acceptable assays are available. The use of choir-positive donors positive for anti-S would minimize the fractionation of HBV-DNA position units in the interval, and preserve levels of anti-HBS in plasma derivatives.

Preliminary data from the Red Cross and Blood Systems, Incorporated, indicate that new highly sensitive surface antigen tests will detect antigen at levels equivalent to approximately genome equivalents per milliliter or higher per donation. This is equivalent to the sensitivity, NAT HBV testing in pools of 100 to more

than a thousand that are currently proposed.

We would consider supporting HBV NAT assays in mini-pools if an ultra sensitive assay were developed and validated in a multiplex format to be combined with the current HIV and HCV assays. NAT HBV mini-pool sizes of 16 to 24 samples as currently performed in the U.S. on whole blood donations for volunteer donors for HIV and HCV may improve HBV detection to 500 to 1000 genome equivalents per mil--per donation, using current technology. This would result in about a five to ten day closure of the HBV window period based on the observed HBV doubling time of 2.5 to 4 days in the pre-surfacing antigen ramp up phase.

The estimated cost for this additional benefit is roughly $36 to $48 million annually in the volunteer sector. Given the current incidence of HBV among U.S. volunteer blood donors--9.5 per 100,000 person years of observation--and this estimated window period reduction by mini-pool NAT relative to highly sensitive B surface antigen assays of five to ten days, we project that the yield of HBV NAT, compared to the unlicensed but more sensitive surface antigen assays will be between 1.3 and 2.6 HBV detections per million volunteer donations per year; that is NAT-positive B surface antigen on an ultra sensitive assay.

From data presented at recent meetings, it appears that the majority of HBV DNA positive, surface antigen

negative units detected in Europe and Japan are found to be positive in tests for antechoir. All volunteer blood collected in the U.S. is screened for antechoir, so detection with HBV NAT will be substantially less than in those countries where such screening is not routine, especially the countries of the European Union.

Most recipient exposed to such units will have sub-clinical, transient HBV infections, with no long-term sequelae. Additionally, as all blood derivatives are subject to one or more highly effective viral inactivation procedures, the goal of testing plasma for further manufacturers to ensure as small as possible a viral load in the starting material. Thus, the practical benefit of mini-pool NAT for HBV is exceedingly poor.

We recognize that the blood community's commercial relationship with plasma fractionators is not of regulatory interest to the FDA. Still, we encourage FDA to give expedited considerations to applications for more sensitive hepatitis B surface antigen testing, both for enhanced safety of the U.S. blood supply, and to help the membership of AABB answer the concerns of fractionators on both sides of the Atlantic.

Thank you.

DR. HOLLINGER: Thank you, Dr. Katz.

And then let's follow this with the comment from

the American Red Cross--Dr. Stramer?

DR. STRAMER: Okay. Thank you. I'll make the comment from here.

I will skip the first two paragraphs. You know who I am, and you know who the Red Cross is.

THe American Red Cross supports the continuing efforts to increase the safety of whole blood components and plasma derivatives, and therefore supports the effort to examine methods to reduce the small residual risk of hepatitis B virus transmission through blood, blood components and plasma derivatives.

Currently the risk of hepatitis B through transfusion from whole blood donations is estimated to be one in 63,000, based on an incidence of 9.5 per 100,000. Those are the figures that Dr. Katz just presented. More recent data from the American Red Cross for 1997 to 1999 demonstrate incidence of 4.5 per 100,000, which reduces the risk to one in 135,000.

Studies performed by the American Red Cross and presented at the last Blood Products Advisory Committee meeting highlighted the low concentration of HBV DNA in seroconverting HBsAG-negative individuals early in infection. The median concentration of virus was reported to be 600 copies per mil, in 13 individuals studied. Of those 13 individuals, five would have been detected by

pooled HBV NAT if one assumes comparable test sensitivity with current HIV and HCV-NAT tests used today in mini-pools. This translates to a window-period reduction of four days of a 25 total--25-day total.

Data were also shown at the BPAC documenting that HBsAG assays having sensitivities of .1 nanogram per mil or less are able to detect samples having DNA copy concentrations in the range of 100 to 8,000 copies per mil, with a median detection of 3,440 copies per mil. This sensitivity is comparable with the sensitivity of NAT testing currently performed in the source plasma industry, using relatively large pools. Therefore, it would seem logical to follow a step-wise pathway to decrease an already small risk from hepatitis B virus as follows.

One--implement sensitive HBsAG assays with a yield comparable to HBV NAT that is performed in large pools of 100 to 1,200 donations; two, develop ultra-sensitive HBV NAT methods, having 20 to 50 copies per mil sensitivity that can be multiplexed with the current HIV and HCV nucleic acid tests in the mini-pool environment.

It is worth noting that due to the low incidence of hepatitis B in whole blood donors, long inter-donation intervals, and therefore the possibility of only one window-period donation from any positive donor, and antechoir screening of all whole-blood donations, that even

upon the implementation of HBV NAT testing the yield will be very low--approximately 1.2 per million, using the Red Cross 1997 to 1999 incidence data.

The American Red Cross's proposed current strategy for the management of hepatitis B virus in the context of manufactured plasma products is designed to assure the absence of detectable HBV DNA in the final products. As I discussed yesterday for hepatitis A virus, hepatitis B virus PCR will be performed on pools of plasma prior to fractionation. In the event of a positive result, the manufacturing pool would not be used and would be destroyed.

Red Cross has performed a qualification run to determine the logistics and feasibility of this strategy. A pilot study involved the equivalent of 540,000 donations that were pooled into 45 manufacturing pools of 3,200 liters. Each pool was tested for HBV DNA by PCR at National Genetics Institute. It is no surprise that all pools tested negative for HBV. Although this strategy allows the detection of only high titre units, there is no evidence that high titre units are not being detected currently.

As part of the strategy, consideration is also being given to HBV DNA screening of antechoir reactive donations, and use of only those units that test HBV DNA negative. We believe that this strategy for HBV screening for recovered plasma from volunteer whole-blood donors is

the most reasonable approach until sensitive pooled HBV NAT methods are available.

Thank you.

DR. HOLLINGER: Thank you, Susan.

Questions? Anybody else from the public wish to make a comment?

Committee members--comments?

Okay. Thank you, Robin.

We're going to move on, then to the next item, which is proposed FDA Guidance on Leukoreduction: the Current Thinking, and Dr. Lee will give us an introduction and background to the issues.

Open Committee Discussion

Proposed FDA Guidance ON Leukoreduction: Current Thinking

DR. LEE: Thank you, Mr. Chairman, and good morning.

I believe you're on the home stretch now. This is the last topic before we adjourn, so hang in there.

This is a topic that we've visited several times before, and we will do so once again this morning, with the aim of shaping a future FDA guidance on this topic: leukoreduction.

Let me give you a brief introductory background about leukoreduction; the regulatory milestones associated with that topic--although much of this is probably familiar

to most of you.

I guess I'll start with the March 1995 FDA workshop on leukoreduction, where the topic of leukoreduction as a process to generate a special class of products was discussed. All of the blood components--cellular blood components, more specifically, red cells and platelets--could be leukocyte reduced for increased product purity, which had certain clinical benefits in--at least at that point--selected, well-recognized clinical cases. And as a result of this workshop, in May 1996 an FDA memorandum was written on the topic of leukocyte reduction, and that memorandum focused on manufacturing issues, and left the use of this class of products to medical discretion for those patients that were recognized to potentially benefit from that product. And that memorandum basically stated that--recommended the specific term "leukocyte reduction" or "leukocytes reduced" as the proper term to use for these class of products; recommended that the residual white blood cell threshold to be no greater than 5.0 x 106 residual white blood cells per unit, that 85 percent of the original therapeutic blood be retained in the leukocyte reduction process, and the whole process be conducted in a GMP setting to assure a quality of the product that are subjected to this process.

The indications for use of those products were

left to medical discretion, and clearly recognized indications were few: febrile nonhemolytic transfusion reactions were one, and that claim made its way into the circular of information which is blood product labeling; a product insert for blood and blood components. And the indications were beginning to be broadened, and the first effort at that was in September of 1997, when the topic was discussed by this committee for the specific indication of whether or not leukocyte reduced blood products are effective in reducing the potential for CMV transmission by blood. And the committee, by overwhelming majority, voted in favor that leukocyte reduction is effective in reducing the transfusion-transmitted CMV, and also noted that the different methods for reducing leukocytes--I'll use the fly as my pointer--

[Laughter.]

--I guess I don't have my pointer any more. That's all right--that the different methods for leukocyte reduction were not equivalent, however all methods were effective, probably to different levels that were too difficult to demonstrate clinically.

Now, one would anticipate that additional discussion about indications for use would be brought to this committee, such as the effectiveness in reducing the potential HLA allonization which complicates patient

management. And, most importantly, the potential for leukocyte reduction to reduce the transfusion-related immunosuppression that has a very significant clinical effect yet--although it is a very difficult effect to demonstrate clinically.

The fact that leukocyte reduction might--the fact that blood transfusion might suppress the immunity of the recipient such that tumor progression or post-operative bacterial infections--things of this sort--can--that effect of transfusion, if demonstrated, can also be diminished by leukocyte reduction if demonstrated--those are very important clinical indications that are currently being discussed, but the magnitude of the clinical trials that are necessary to demonstrate these effects is such that it is probably not possible to demonstrate that effect in a reasonable--in reasonable recent future, other than by consensus of accruing experience over time.

Nonetheless, that's an important indication, and along with many others, those indications could have been discussed. However, that topic was sort of short circuited. In September of 1998 this committee was charged with the question of whether or not leukocyte reduction is effective in--whether or not universal leukocyte reduction--that is, the use of leukocyte reduction for all red cells and platelets at least--would be a scientifically sound thing to

do, in view of the fact that it has several clear-cut, demonstrated clinical benefits and a whole multitude of other controversial, yet nonetheless important, clinical indications.

And this committee supported, by overwhelming majority, that on a clinical, scientific basis, that leukocyte reduction is to be recommended for all cellular blood products; more specifically, red cells and platelets.

Based on that outcome, in December of 1999, FDA sponsored a public workshop on the implementation of universal leukocyte reduction as to how this transition might be best accomplished. Of course, the scientific issues are not the only ones affecting leukocyte reduction, and in April of 2000 the PHS Advisory Committee discussed the issue of reimbursement; that is, although it is clear that scientifically this is desirable, on a broader public health level is it also desirable, given that cost is an important concern, more specifically reimbursement is an important concern which might have detrimental indirect effects if universal leukocyte reduction were to be hastily implemented.

And, to close the loop, in June of 2000 this topic was brought before the Transmissible Spongeform Encephalopathy Advisory Committee with respect to the effectiveness of leukocyte reduction in reducing the

potential infectivity of variant CJD. The charge to BPAC in September of 1998 was to consider all clinical indications except CJD, and that last topic of CJD was brought before the TSE Advisory Committee in June of 2000, and that committee found that the current existing evidence was insufficient to conclude that leukocyte reduction is effective in reducing the potential infectivity of variant CJD by blood transfusion. That was no surprise. We anticipated that, but at least we visited the topic thoroughly, and we know exactly where we are, given the amount of information available.

And here we are today, in trying to shape an FDA recommendation--FDA guidance to industry about leukocyte reduction, as to how we might now proceed forward, given this amount of discussion, and this amount of information that is currently available.

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Just to pick up where we left off in September of 1998, this committee voted 13 votes "yes," "no" votes zero, with three abstentions to the following question: is the benefit-risk ratio associated with leukocyte reduction sufficiently great to justify the universal leukocyte reduction of all non-leukocyte transfusion blood components, irrespective of the theoretical consideration for transfusion-transmitted CJD. And both the consumer and

industry representatives voted--were in agreement with the "yes" vote; and just to remind you, the cost and reimbursement concerns were not considered by this committee.

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And this scientific decision was then further developed at the FDA workshop--as I briefly alluded to just awhile ago, and three predominant themes were discussed at that FDA workshop in December 1999 on implementation of the universal leukocyte reduction. We talked about the transition period, as to how we might--given that this is to be desirable--how we might best go about making the transition period, and generally the workshop participants favored a transition period of something like two years, where people are getting ready for a ramp up, making changes to their operating procedures, their personnel, adjustments to their scope of manufacturing to accommodate increased use of leukocyte reduction.

At that workshop, another theme that emerged was that the current method of monitoring the quality of leukocyte reduced blood was insufficient; that the current recommendation, which is really meant to be a minimum FDA recommendation, but nonetheless taken as the recommendation of testing only 1 percent, or four units per month, per process variation of leukocyte reduction, that was felt that

that method is grossly insufficient to assure the quality of leukocyte reduced blood.

The third theme that emerged was that of streamlining licensing. The workshop participants agreed that the current mechanism of licensing blood centers for leukocyte reduced blood could be streamlined so that reporting burden is diminished, without necessarily jeopardizing public health.

So, having said that, I have identified three issues--three fundamental issues; there are whole slew of--at least several dozen specific issues that can be discussed, but we only have this morning, and I think these three fundamental issues are plenty for discussion, and it will actually be very helpful if you can actually derive some kind of a direction based on this morning's discussion.

The first--and I take this in the order of increasing complexity, and reserve the most complicated question for last. Starting out with a manufacturing issue, and that is an issue of quality monitoring. How can we better assure the quality of the leukocyte reduced blood, in accordance with the previous discussions; the current recommendations that are meant to be minimum are adhered to as the recommendation are clearly insufficient.

The next issue is that of licensing, and how we might streamline the licensing of leukocyte reduction.

And, thirdly, we can again revisit the dilemma of leukocyte reduction as a clinical choice or as a manufacturing requirement, and we'll see how much--what kind of a resolution we can bring to that current dilemma.

Okay--so this is the first major topic--major sub-topic of leukocyte reduction for this morning. And in order to discuss this thoroughly, I think we might start with a definition.

We talk about pre-storage leukocyte reduction. I think we might begin with a definition so that we're all on the same page. And this is a working definition, which can certainly be modified. And I'll read this definition: the reduction in the content of contaminant leukocytes in a blood unit to 1.0 x 106 cells or fewer while retaining at least 85 percent of the therapeutic product within 24 hours, using a method which assures, at 95 percent confidence level, that more than 95 percent of the units meet these product specifications.

That's a long definition, however it has some key words in it which are highlighted in orange. First of all, the word "contaminant." I put that word in there to indicate that we mean blood components that are meant to be non-leukocyte blood components; certainly, granulocyte is a blood component and is excluded from this definition. So we're talking about red cells, platelets and, potentially,

plasma, because they are blood components and leukocyte contaminants are present--to very low levels, but nonetheless still present in units of plasma. So, first of all the word "contaminant" appears in this definition.

Secondly the threshold of residual white cell content per unit currently reads, in this definition " 1.0 x 106," whereas before, per the 1996 memorandum, which is still in effect today it's 5.0 x 10 to the sixthXXXX. And this is an adjustment that can easily be made, because we know that we can get there with the current filtration technology. This is the standard that's being used by Europe. And really, from an operational standpoint, it is not much different from 5.0 x 106, but this is a slight change towards increasing the stringency as the technology permits. So therefore 1.0 x 106 was chosen.

Retention of product--85 percent. This is a carryover from the previous memorandum. There is really no reason to increase--although I suspect that we could. But, for the moment, I decided to retain this 85 percent. Certainly this can be discussed further by this committee today.

So the 1.0 x 106 and 85 percent, those are numbers that are geared at increasing product purity and product safety, while retaining product efficacy.

Now the word--the time frame of this process

"within 24 hours of blood collection." A variety of different time frames can be chosen for this. The committee might be well reminded that the current leukocyte filtration equipment, or more specifically, blood filters and cytapheresis instruments--well, I guess more specifically, blood filters--they had been approved under 510(k) for pre-storage leukocyte reduction for periods that extend up to five days. So--we don't want to say five days, however, because clearly five days would be a fairly long period, and it's not really pre-storage anymore if a product has been sitting around for five days, then leukocyte reduced. Yet, operationally, any time period more stringent than 24 hours would be nearly impossible, and even 24 hours might be too burdensome operationally. But for right now, we might go with the 24 hour as a working definition so that we can minimize cell degradation and cytakine release which contributes to adverse transfusion effects.

And lastly, but most importantly, to process a unit of blood for leukocyte reduction in a way that assures, with a certain level of confidence--and what is that level of confidence? Typically what's been used in clinical trials is 95 percent, so we have consistent with that 95 percent confidence level was chosen. And what is the process specification? With the product specifications--if product specifications are defined as 1.0 x 106 residual

cells, with 85 percent of product recovery, then what are the process specifications? You might say that the process specifications is assuring that 95 percent--greater than 95 percent of the products subjected to this method are actually acceptable units, and you know that to be the case with 95 percent confidence. And those two numbers are meant to be--meant to define the process specifications.

Next slide.

Okay. So we have--that definition does not necessarily mean that--i's not necessarily recommended as the one--as the final definition, but certainly recommended just as a starting point for discussion.

Okay. Now, let's move to a case example. Just to illustrate why current methods of QC testing, or quality monitoring, is insufficient to assure product quality of leukocyte reduced blood.

Let's go through this case example.

A blood center manufactures and leukocyte reduces 400 red blood cells units per month. Let's say that an error in filter priming procedures used by a new staff member results in achieving acceptable final product standards in only 80 percent of leukocyte reduced units. Per current FDA recommendations, the blood center performs QC testing on four units, and the units are found to be satisfactory. That's entirely possible; with a process

specification of only 80 percent it's entirely possible that when you test four units, you might come across four units that are quite acceptable.

So what is our sensitivity in detecting that a procedural error has crept in and is jeopardizing many units as unacceptable units? Well you might calculate that by taking 80 percent--.8--and raising that to the fourth power for the chance of occurring an acceptable unit four times in a row, and that overall chance of seeing four units that are acceptable, consecutively, is 41 percent.

Now if that's 41 percent, then 1 minus 41 percent, or 59 percent, is your chance of detecting at least one unit that is unacceptable. Now, notice I used .8 raised to the fourth power than .2 raised to the fourth power because .2 raised to the fourth power would mean detecting an unacceptable unit four times in a row, and we're not interested in that statistic. We're interested in detecting at least one unit, so we have to go with 1 minus .8 raised to the fourth power for a 59 percent figure--which is really the test sensitivity if you consider the entire quality control and monitoring process as a test, then you might say that the sensitivity of this test or this quality monitoring program is 59 percent, which is really not sufficient at all. And in this case I've defined that sensitivity as your confidence level in assuring the quality of leukocyte

reduction process.

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So as you can see that the current methods are grossly insufficient, grossly insensitive, and does not assure, with any level of confidence, that when you see acceptable units only in your QC testing that the entire process is working properly. That assurance cannot be obtained.

Then we have to define some process specifications in addition to product. I said before that the product specifications are 1.0 x 106 residual cells per unit, and the recovery of 85 percent of the product. And then, once again, the process specifications are that the percent of units that are acceptable be greater than 95 percent, and that we know this to be the case with 95 percent confidence that greater than 95 percent of the units are acceptable. So those are process specifications on top of the more familiar product specifications.

To achieve these specifications, we have to increase our sample size. And we have to do so in a way that's not overly burdensome for blood centers. And sample size is closely related to the concept of a manufacturing period. Obviously a large blood center has a large sample size, and a small blood center will have only a small sample size. However, if given enough time, a small blood center

will make lots of products, too. So we can't just think about sample size as a number, we have to think of it in terms of the time period, therefore the concept of manufacturing period becomes important. And in order to detect a procedural error as early as possible, whatever sample size is chosen, that sample size be divided in multiple alloquots, and that testing be performed as frequently as possible within practical limits so that any error in procedure can be detected at the earliest possible time.

Okay. Now, this chart is meant to be a chart full of numbers of confidence levels, or sensitivities of the quality monitoring program. Across the top are numbers which represent the percent of units that are acceptable. So 50 percent, 60 percent, on up to 99.9 percent, that are the percent of units that meet product specifications of 1.0 x 106 cells per unit or less, and 85 percent product recovery. And along the left-hand column are the number of QC units that might be chosen.

The case example that I went through just awhile ago--if you read across to 80, and then drop down to "4" for QC units, you see the number "59," and that's the 59 percent confidence level, or sensitivity, which I just explained.

12:35 And, recognizing that that is grossly insufficient, what would we like? Well, we just defined, at

least for the purposes of discussion, 95 percent confidence level, with 95 percent--more than 95 of the products meeting product specifications. So if you move across the top column to 95 percent, and then drop down to 95 percent confidence level, and then read of the left-hand column of the number of QC units, we arrive at 60 unites. So it appears if you quality control 60 units and do not find any unacceptable unit in your 60--pool of 60 samples, then you can be assured that more than 90 percent of the products that you claim as leukocyte reduced are indeed leukocyte reduced, and you can make that claim with a 95 percent confidence level. So this is a way to put a handle on the amount of uncertainty that necessarily accompanies the fact that you're not testing every unit. If you're not testing every unit, there's always room for some uncertainty, but this way at least your know what the level of uncertainty is.

Now, that chart that I just went through is really for conceptual purposes, and it's not rigorously accurate. In fact, as you decrease the number of sample--as you decrease the total number of samples, or total number of units that a particular blood center manufactures, the number of units becomes a little bit smaller than 60. So if you make 250 units or more, I think if you test 60 units the process specifications hold. However, as you drop down, the

number of units that you actually need to test is slightly smaller. Now, you might argue that this is not significantly different from 60, and that's a point that can be discussed further, but there is some small reduction in the actual number of units that you have to test if you are making less than 250 units.

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Now, of course, as I said earlier, the sample size has to be considered in terms of the manufacturing period or some kind of time interval. Now if you define your time period or more frequent, then the QC burden becomes quite high. Now, if you define your time period as ten years, then the QC burden is very, very low, but then you won't know where you're at for a ten-year period. Only after a ten-year period has elapsed you'll know that whatever you did is whatever the process specifications you're aiming for. So we have to strike some sort of a balance. And for purposes of discussion, we chose three months. Anything more frequent than three months would be fine, but recognizing that this may be a significant QC burden, chose three months as the upper limit.

And as I alluded to earlier, there are advantages of a long manufacturing period; the longer it is, the smaller the QC burden, obviously. The 60 units can be spread out over three months is less burdensome than 60

units spread out over one month. There is a price to pay for that, however, and that is the duration of uncertainty. If you choose a short time period, such as one month or shorter, with each passing of that time period you know for sure that you've closed the loop; everything you've done, provided that you haven't encountered an unacceptable QC unit is per process specifications and all product specifications are met. You know that at the end of that manufacturing period. If you choose a long period, that uncertainty continues until you close the loop by completing QC testing for that period. And, of course, if you were to uncover--discover an unacceptable unit, then you'll have to perform some kind of investigation, not only to correct the process, but to initiate action for all the products that had been released under that process, in terms of product retrieval and notifications. So the chances of that becomes higher with lengthening the manufacturing period. So this is a trade-off.

And whether you choose a short period or a long period depends on your manufacturing scope. If you're a large blood center QC burden is relatively small with respect to your entire manufacturing production capacity, and you might go with a reasonably short manufacturing period; whereas if you're a large blood center--sorry--whereas if you're a small blood center, you

might choose a longer period just so that the QC burden does not overwhelm your operation.

Whatever the sample size is, and whatever the manufacturing period is chosen, the number of total units that are subjected to QC testing should be divided so that testing can be performed at weekly intervals or more frequently, towards the aim of detecting an unstable process as early as possible. So although finding a portion of the units acceptable does not assure that you're okay with your process, finding something certainly tells you that something is not okay. And to increase that possibility of detecting as early as possible, you might divide that into multiple alloquots and test them periodically.

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In terms of process validation, right now the Agency looks at the quality monitoring program as a two-phase effort, and this is a concept that carries over from the previous 1996 memorandum that's still currently in effect. You might initially validate your process by testing a certain number of units up front, consecutively and, as per previous discussion, that number may be 60 consecutive units per process variation, and when you discover no unacceptable units, having directly QC tested 60 units consecutively, then you can be assured that, at least for the time being, your process is robust.

How do you ensure that your process remains robust for the next ten years, or as long as you manufacture leukocyte reduced products? That's where you have to perform continuing quality monitoring through quality control testing, and this depends on the--as I stated just awhile ago--predefined sample size, and predefined manufacturing period. And these are criteria that are facility-specific, and you may choose your own, depending on your manufacturing scope.

If every unit that you initially test as part of process validation, and then you subsequently test as part of continuing quality monitoring, if all the units turn out to be acceptable per QC testing, then everything is fine. But, of course, you will not. You will encounter an unacceptable process every now and then. And that point, revalidation of process will be necessarily.

But even without encountering an unacceptable unit, you might just change your process, just because new technology became available, you are now able to hire an increase level of staffing. Whatever the change is, if you introduce a change, you should revalidate the process anyway. Even if you don't change your process, if you encounter an unacceptable unit, then you should also revalidate your process.

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So--either a change in the process or discovery of an unacceptable unit triggers revalidation. If the revalidation is being performed as part of having detected an unacceptable unit, then, of course, that has to be preceded by process investigation; you have to look to see where you--if your process went wrong somewhere. And if you find it, of course, you will correct it and revalidate.

Even if you don't find anything, you'll have to revalidate before you can determine that the unit that you detected as unacceptable is sheerly by chance; everything is fine; your process is fine, however, since your process specification to begin with is only greater than 95 percent, not 100 percent, then you might encounter a product that's still within your process specification, it's just on a statistical chance basis. Before you can arrive at that conclusion, you should revalidate another 60 consecutive units.

So the need for revalidation--you might think that, based on chance, you might stumble onto an unacceptable unit so frequently that you're revalidating all the time. That is not necessarily true. The need for revalidation is unlikely if your process is stable, and that your process standard--whatever it is--exceeds the minimum standard significantly. The minimum standard that we just talked about is 95--more than 95 percent of the product

being acceptable. If you operate very close to that standard, then, yes indeed, the chances are high that you might, by chance, encounter an unacceptable unit and subject yourself to a process revalidation requirement. However current filtration technology allows operating at a standard much higher than that. I suspect that it's easily 99.9 percent. And under that scenario where you are exceeding the minimum standard by at least 50-fold, and provided that your process is stable, your need for revalidation is highly unlikely.

So, I just kind of, step by step, went through what might be a reasonable alternative, in terms of quality monitoring--alternative to the ones that are in place today.

So let's consider other alternatives. Well, the first alternative is to simply retain what we have--four units or 1 percent, whichever is greater, per month. The problem with this, of course, is that it does not assure product quality. But it is simple, and it's already in place, and it's a reasonably low QC burden.

An alternative to this might be to simply increase this number. While this is also simple, an the transition for that would be easy, and it would likewise be a relatively low QC burden, however it's only a marginal improvement in assuring product quality, and you won't know how much you've improved.

You can make a drastic change. You could switch to device QC testing. Yesterday we talked about 510(k) notification not being subject to product-release requirements, whereas PMA is. Currently, blood filters are clearly under 510(k). There is--typically, there has not been a clinical trial requirement, and once cleared, typically there is no continuing requirement from the filter manufacturer to demonstrate continuously that all filters are manufactured according to product specifications.

If we were to increase the burden, or shift the burden to the device side, that might potentially relieve the blood centers of having to perform any QC testing, since QC testing is being done up front by the device manufacturers. That's a drastic change, and I point that out only for discussion, not necessarily as the Agency's current thinking. The problem of that approach, of course, is that everything that happens after the filter--all the variables that are operational, that are associated with training of the people that are actually performing leukocyte reduction at the blood center, those are all variables, and none of that would be captured under that kind of paradigm.

In addition to these three alternatives, the fourth is the one that I just went through in great detail. The problem with that is that QC burden is high, especially

for small centers. But, actually it can be quite low for large centers, not requiring 1 percent anymore, but requiring simply 60, provided that you make enough products within a reasonably short time period, that 60 may turn out to be below 1 percent. The advantage of this is that it gives you statistical confidence, and it tells you exactly where you are in assuring minimum standards.

Next slide.

So, I think this sub-topic deserves an interim summary. So, in terms of quality monitoring, we're shooting for statistical confidence of an acceptable process. The process performance might be defined as better than 95 percent of acceptable units. The confidence level might be defined as 95 percent, and this is to be implemented with respect to initial process validation and continuing quality monitoring. Important concepts to incorporate in implementing such a plan would be the sample size and the definition of the manufacturing period. An the process investigation is necessary whenever you discover one--even just one--unacceptable unit, and revalidation will be needed.

Alternative to this process are either retain the current approach, or shift the QC burden to the device side and accept the operational variables that exist at the blood centers.

Next slide.

Okay. So I thought that was the most straightforward and least controversial and least complex of the three questions that we want to discuss. The second is the licensing paradigm. And although this is more complex, I have less to say about it.

Per 1996 memorandum, currently require up front submission and review of the following elements: quality control data, labelling, standard operating procedures, manufacturing records, and all of those are elements--and those are the major elements; there are others that are minor--those major elements are to be submitted up front as prior approval supplement--or PAS--for all submissions requesting licensure of leukocyte reduction.

The proposed revision is as follows: retain the requirement for submission of quality control data and product labelling, however drop the remaining, and simply require evidence of quality assurance oversight, and the reporting can also be expanded. Not all submissions need to come in as prior approval supplement, but may be submitted in one of three ways, depending upon what it is--what situation fits you best.

One might be CBE, or "Changes Being Effected." If a blood center implements leukocyte reduction per FDA recommendations, FDA recommendation can be regarded as a

protocol of leukocyte reduction implementation, and if you're following that protocol then you may simply implement at the same time that you report under licensure. So that would be a CBE licensing. So you'll be submitting less, and you will be able to implement your change quicker.

However, if you were to deviate from these recommendations and propose an equivalent or better manufacturing recommendations, those submissions are certainly welcome. But in order for FDA to agree with you, we would have to see that submission up front, an we would review them in detail. Under that scenario, we would fall back to all of the previous submission elements to be submitted, and require and up front review as a prior approval supplement.

For blood, there are often multiple sites that are under control of a single applicant, but typically, multiple sites under the control of a single applicant uses the same SOP, uses virtually the same everything except for the fact that they're at a different center. And for those centers, you might simply report under CBE, if you do not deviate from the current protocol--from the FDA protocol. But if you do deviate from the FDA protocol, then your protocol needs to be submitted as a prior approval supplement for up front review. But once reviewed and accepted, the addition of multiple sites under that protocol can be reported as

CBE. And this would be the "Comparability Protocol Mechanism."

Next slide.

Let me go over two pieces of regulation that we think will allow us to do this. Under 21 CFR 61.112(c), the changes being effected in 30 days is first described--and I'll get to CBE in just a minute, but this is a broader rule that subsumes CBE; CBE 30 subsumes CBE.

And CBE-30 reads as follows: "A supplement shall be submitted for any change in the product, production process, quality controls, equipment, facilities or responsible personnel that has a moderate potential to have an adverse affect." So if you have a significant affect, that's a PIS, if it's a minor affect, it's something even less than CBE 30. If it's a moderate potential to have an adverse affect on the identify, strength, quality, purity or potency of the product as they may relate to the safety or effectiveness of the product, that's a CBE 30.

Now, under this rule, CBE is explained further. "FDA may determine that, based on experience with a particular type of change, the supplement for such a change is usually complete and provides the proper information, and particular assurances that the proposed change has been appropriately submitted, the product made using the change may be distributed upon receipt of the supplement by FDA."

So, under the case of CBE 30, when experience has shown that submission requirements are typically met, the FDA has the option of designating that as CBE.

This rule goes on further to say, "These circumstances may include substantial similarity with a type of change regularly involving a CBE supplement of a situation in which the applicant presents evidence that the proposed changed has been validated in accordance with an approved protocol." So this allows the comparability protocol provision for multiple facilities, while at the same time this may serve as the basis for viewing FDA's guidance to industry as leukocyte reduction as a protocol which allows CBE submission to be made under that protocol, if you follow that protocol.

And I tried to summarize this in a chart. On the left-hand column are the submission elements, and across the top are the different mechanisms of submission. For PAS column--now this is referring to PAS submitted as an alternate to FDA's guidance. If you deviate from FDA's guidance--you're certainly welcome to do so, but it has to be a PAS submission for up front review and approval. And under that submission you would include all the elements that are x-ed for FDA's close review.

Second two columns is for comparability protocol. If you have multiple facilities and you want to deviate from

FDA's guidance, you're certainly welcome to do so, but you should first provide a protocol. And in that protocol, you should include the elements that are x-ed for FDA's up front review and approval. Once reviewed and accepted by the FDA, then you may report much less for multiple facilities under that protocol, as CBE. And that includes the product labeling, quality control data, and manufacturing records.

If you do not deviate--if you simply follow FDA's guidance to the letter--then that can abe viewed upon as a protocol itself which allows the applicants to submit simply product labelling, quality control data, and manufacturing records in support of a CBE submission; you're implementing the change at the time you're requesting licensure.

Next slide.

I think that's straightforward enough that I did not do a summary for that, and I'll move to the most complicated question, but I have the least to say about that.

And this is the issue of product use. Is it a clinical choice, or is it manufacturing?

In the 1996 memo, per outcome of the '95 workshop, leukocyte reduction was left as a clinical choice, a medical decision to be made. Physicians may choose from available products, both leukocyte reduced and leukocyte not-reduced. The proposed revision is as follows--once again, the

decision to use leukocyte reduced product remains a medical decision. Once again, both leukocyte reduced and non-leukocyte reduced products will be available. "If a physician chooses to use a non-leukocyte reduced product for a particular patient he may do so, and the product should be available. However, the clinical benefits of leukocyte reduction have been clearly recognized and the indications for using them are continuing to expand. In recognition of that, FDA encourages the use of leukocyte reduced product whenever feasible."

Let's talk about that just a bit further. Pre-storage leukocyte reduction, as we defined about 20 minutes ago, and let's consider the clinical benefits of increasing product purity through leukocyte reduction. These--the four indications that are listed up at the top, that much we already know. Pre-storage leukocyte reduction is superior to bedside filtration, and there is no controversy about that. It eliminates much of the inconsistency that accompanies a bedside procedure, and also it eliminates the often--the clinically very significant, although relatively infrequent, consequence of precipitous hypotension that has been associated with bedside filtration.

In addition to that, the potential to virtually eliminate febrile reaction is well recognized through

pre-storage leukocyte reduction, but no necessarily by bedside filtration. The potential to reduce CMV transmission, perhaps comparable to the level of CMV seronegative units is clearly recognized. The potential to reduce HLA alloimmunization is clearly recognized.

And let me skip down to the bottom, with the orange print, to further argue in favor of using leukocyte reduced products whenever possible.

Although arguments against leukocyte reduction as a routine use has pointed out that not every patient benefits from leukocyte reduced blood, and on a cost consideration, this should be reserved for only those patients that are recognized to be beneficiaries, the following arguments can still be made. Why should patients suffer through several transfusion reactions before being recognized as a candidate? Second question: HLA alloimmunization may not necessarily be important for current patient management, however you never know what's going to happen to that patient in the future. He may receive a transplant in the future. So we should probably try to minimize that for all patients.

Also, even if everything works out perfectly, in terms of recognition, there are medical and clerical errors. A physician may order leukocyte reduced blood, yet a leukocyte un-reduced blood may be sent to the floor. A

patient may not recognize the need for leukocyte reduced blood when it's clearly indicated, and not prescribe it. So there are errors that can be eliminated by routine use.

And, lastly, there are a whole slew of indications that argue in favor of routine use, and although they remain controversial at present, we might consider those as a precautionary measure, even for these controversial indications. And let's just quickly go through that in the middle part of the slide. And those are: transfusion associated immunosuppression--a very important effect, almost impossible to demonstrate through clinical trial, but a very important effect; red blood cell and storage lesion--a very important effect in terms of product manufacturing and product shelf life; bacterial growth during product storage--although not clearly the sole answer to the problem of bacterial contamination, perhaps a partial answer; leukocyte-induced viral reactivation--another important consideration; as is transfusion-related acute lung injury--re-perfusion injury after cardio-pulmonary by-pass procedures; and even the theoretical transmission of CJD and variant CJD. TSE advisory committee found the data is insufficient. The advisory committee did not conclude that it is ineffective. It simply found that data was insufficient to recognize effectiveness at this point.

Next slide.

Are there any drawbacks, other than cost, of leukocyte reduction? There are, but those are filter-specific--device specific. These are reactions that are caused by filter failures, and provided that there is enough scrutiny at the device manufacturing level, these can be avoided. So far, two reactions have been reported, and this is the red-eye reaction, I think most everyone in the audience is familiar with. There's been more recent reports of severe back pain associated with the use of certain filters, and the circumstances around that is even less clear than the red-eye, but nonetheless recognized as a potential complication of filter failure.

But even with these failures, the numbers are small, and the problems were readily controlled by withdrawing particular lots of filters.

So, in terms of FDA's current thinking on the use of leukocyte reduced blood components, they recognize the advances in scientific understanding with respect to leukocytes in transfusion medicine. The indications for leukocyte reduced blood products are growing all the time. And whether or not it's effective in reducing variant CJD really remains unresolved at this point.

With respect to reimbursement, we recognize this as the only, but very significant concern, and this problem is being addressed at the Department level, with the PHS

advisory committee as the focal point. Of course the key player is our sister agency of Health Care Financing Administration. But these efforts are aimed at minimizing the potential adverse impact on transfusion safety, if routine use were to be implemented without thorough investigation.

So the Agency continues to recognize both leukocyte and non-leukocyte reduced products, however the agency supports the use of leukocyte reduced products whenever feasible.

You might ask when will leukocyte reduction become a manufacturing requirement? Well, I guess there's two ways that this can become a manufacturing requirement. The first is the most obvious, straightforward one, and that is if the agency moves towards changing the Code of Federal Regulations to recognize leukocyte reduction as a manufacturing step--as an integral manufacturing step in the collection of blood; much like testing for HIV. If that happens, then it is a regulatory requirement and is directly enforcement all GMP.

There's an alternate pathway. The industry might beat FDA to the punch; might decided that there is enough to go with leukocyte reduced product, and adopt, as a voluntary industry standard, the use of leukocyte reduction for all patients. In that case, it is not a regulatory requirement

per se, however, once it is clearly recognized as the industry standard, it will influence the agency's review decision, in terms of licensing--licensure submissions and review.

You might think, "Why not move directly to rule-making?" Well, of course, there's the cost concern, and there's the potential for indirect adverse impact on a large scale of reducing transfusion safety. And, much as a physician is taught not to do harm before that physician intervenes in the management of a patient, I think the same might be true for regulatory actions: do not over-regulate when you don't have to, unless you're clear that the regulatory action will be beneficial.

So that's sort of where things are. And I guess at this point I will try to entertain some questions.

DR. HOLLINGER: Thank you, Dr. Lee, for this--what I think is a well thought out and presented--the issues that are available. Appreciate that.

Yes, there are some questions. There are some groups that want to speak to this issue from the public, but let's--what I'd like to do, maybe have them just talk just a minute, and then we'll come back to that.

OPEN PUBLIC HEARING

DR. HOLLINGER: There are two groups that have asked, again, to speak. One, again, is the American Red

Cross--Dr. Stramer, and is Susan--I'm sorry, Dr. Chambers--Dr. Linda Chambers from the American Red Cross.

DR. CHAMBERS: Since I'm relatively new to these meetings, I will read my first paragraph, but beg your indulgence.

Thanks for the opportunity to speak regarding leukoreduction of red cells. I'm Dr. Linda Chambers, the Senior Medical Officer for the American Red Cross Biomedical Headquarters. Red Cross, as you know, collects over 6 million units of blood from volunteers each year in the United States, and is responsible for almost half of the nation's blood supply.

In September '98, when BPAC voted in favor of leukoreduction of all cellular transfusion components, the Red Cross received a powerful message and took this as a unanimous recommendation to convert our manufacturing processes to universal pre-storage leukoreduction. We began this process as soon as it was feasible for two specific reasons. First, Red Cross is a very large organization; we had to convert 36 regions, with physically different manufacturing sites. In some instances, facilities had to be remodeled and extensive new equipment designed and purchased. We also needed to develop new procedures and conduct training for thousands of staff involved.

More importantly, we regarded it as an ethical

responsibility to the patients we serve to help move transfusion practice as quickly as possible to this emerging standard of care. In November of 1998, during our initial assessment of the implications of the BPAC vote, about 13 percent of red cells Red Cross distributed were leukocyte reduced at the request of the ordering hospital. Six months later, and before Red Cross leukoreduction initiatives had been implement, that number had risen to 25 percent; in other words, the requests for leukocyte reduced products were increasing, even before our conversion efforts were fully underway. At the end of April 2000, approximately 56 percent of red cells distributed were leukoreduced.

Red Cross supports BPAC's 1998 decision and believes we've taken the right steps to increase the use of leukoreduced products. We support FDA's intentions to issue guidance and regulations on this matter for several reasons.

First, a specific statement describing leukoreduction as a requirement would enhance the public's confidence in FDA. A document and related regulations would provide strong reassurance that the agency is maintaining their vigilance over the safety of the blood supply and the purity of these products.

Second, a guidance is needed to help ensure that the product being manufactured meets quality expectations.

An FDA directive will help guide standardization across all manufacturing process sites in the quality control procedures, and establish appropriate expectations for FDA inspections. All blood programs will have a more uniform understanding of the measures that must accompany appropriate manufacturing practices and can plan accordingly.

It would be helpful to Red Cross to have clarification of FDA's intentions and expectations. As you can imagine, implementing universal leukoreduction in our manufacturing practice is a resource intensive effort. The longer FDA takes to issue its proposal, the more resources we expend in a direction we believe is appropriate, but that may not be exactly as expected by FDA.

And finally, an FDA guidance document and related regulations will serve to clarify for customers the deadlines and other specifications around which leukoreduction is being performed.

Thus, we ask that the Committee affirm its recommendation for leukoreduction of all cellular components for all patients, and we encourage FDA to take specific regulatory action by issuing related guidances and rules as expeditiously as possible.

Thank you for the opportunity to speak, and I'll be happy to answer any questions.

DR. HOLLINGER: Thank you.

Yes--Dr. Schmidt?

DR. SCHMIDT: Question--is this--in monitoring the quality of the units, the Red Cross sacrifice whole units to do the testing, or does it get alloquots from the units to do their testing?

DR. CHAMBERS: I don't know. Is there someone here from Red Cross who can answer that question?

I believe it's alloquots.

DR. LEE: Yes, I'm not Red Cross, but I know that it's simply alloquots. There are sterile tubings that are already attached to the blood units, and you simply express to the blood in the tubing into the unit, mix the unit up, and let it fill the tubing back up. Then you take the tubing off--all sterilely. So the product integrity is not breached when you take a sample off of it.

DR. HOLLINGER: Thank you.

The next person who would like to speak in the public portion of this is Dr. Merlyn Sayers, for America's Blood Centers.

DR. SAYERS: Thanks, William.

America's Blood Centers' position on universal leukoreduction is simple: if implementation is required, then ABC is going to participate and comply.

ABC members provide something like one-half of

this nation's blood supply, and the membership agrees that many patients might benefit from leukocyte reduced products. And it's even possible that patient outcomes from universal leukoreduction, and those that--we've heard of them from Dr. Lee--those outcomes might even offset some of the costs of universal leukoreduction, and those costs are estimated at somewhere upwards of $500 million. Obviously that offset would take some period of time to achieve.

Nonetheless, the data showing offsetting benefits are inconclusive, and for that reason there's no consensus regarding the value of universal leukoreduction among the membership of ABC. Many members still consider the selection of components for specific indications to constitute the practice of medicine, and thus outside the purview of the FDA.

If the FDA does go forward with a recommendation for universal leukoreduction, ABC has several implementation concerns. Firstly, the issue of reimbursement. The major impediment to implementation of universal leukoreduction is the delay in reimbursement adjustments for Medicare and Medicaid, and they pay for over half of all blood transfusions. Hospitals tell us loudly and clearly that they cannot wait two or more years for reimbursements to catch up with practice, and the time between an FDA recommendation and adjustment of reimbursement has to be

shortened. The Health Care Financing Administration has the authority to do this. Unless a public health emergency exists, FDA must coordinate the timing of its recommendations with increased reimbursement from HCFA.

New recommendations for blood safety should, then, have two components: an FDA recommendation for implementation, at the same time as a HCFA approach for reimbursement, and ABC believes that a recommendation for universal leukoreduction should be the subject of a joint message from the Health Care Financing Administration and the FDA.

Then there's the concern about the implementation period. While universal leukoreduction does have some patient benefits, it is not a compelling public health concern. And in addition to the reimbursement considerations, ABC is concerned that an FDA recommendation concerning universal leukoreduction does have some impediments. For example, there already are spot shortages of filters, and a short implementation period is going to aggravate those shortages. Also, the logistics of providing filtered platelets from whole blood units have not yet worked out, and a short implementation period may create serious platelet shortages because random donor platelets would not be available.

Taking all this into consideration, ABC believes

that any recommendation for universal leukoreduction should allow sufficient time for these issues to be addressed both nationally and locally.

And then, from a logistical point of view, any recommendation from the FDA should allow blood centers to design the implementation criteria that best serve the needs of patients in their community, and allow emerging knowledge to be quickly incorporated into current practice. In simple terms, ABC membership asks that any recommendation from FDA specify the goals and standards, but leaves implementation criteria to be worked out between filter vendors, blood centers and hospitals.

And, finally, FDA's recommendation must be published as formal guidance or as a regulation. Anything less sends ambiguous statements to the public, to the blood industry, to hospitals and to the health care community; and anything less than formal guidance or regulation will make it far more difficult for hospitals to obtain proper and timely reimbursement from third-party payers.

Thanks.

DR. HOLLINGER: Thank you, Merlyn.

Is there anyone else from the public that wishes to make a statement?

Yes--please. And state your organization, name.

DR. DUMONT: I'm Larry Dumont. I'm with Gambro

BCT, and also a member of the Biomedical Excellence for Safer Transfusion Committee of the ISBT.

These comments are not on behalf of either of those organizations.

First, I'd like to congratulate Dr. Lee for his, I think, excellent handling of a very complex, difficult subject. And I've been working in this area for several years, and I believe that his proposal is definitely a step in the right direction, and brings some rigor and clarity to these difficult issues.

A couple comments that I would like the Agency to consider in their final document, whatever that might be--first of all, in the definition of "pre-storage," where you mention--"pre-storage leukoreduction should happen within 24 hours," I think in many cases, that might be logistically very difficult for some blood centers. And I would suggest that the data available does not support that. In fact, 48 hours or some number like that might be better.

First of all, there's--certainly in red cells, there's no significant increase in cytakine production, and even the studies that have been published in platelets that are held at 22 degrees, there's no significant rise in cytakine production until after 48 hours. As far as degranulation or apoptosis in granulocytes, I think there's very little data on that at all. So that I would suggest

that time frame be reconsidered.

Secondly, the data presented, as far as quality monitoring with respect to sample sizing--actually I've seen a lot of those tables before, so they look pretty familiar. But I think--I wanted to remind the Committee that this is a--what could be termed a "non-parametric" approach, that's strictly a pass-fail. And it definitely does have application in this arena, but that's driven by one's own definition, I think, locally of what a failure is, or their approach--also driven by the measurement method that a particular blood center may choose to implement to look at number of white cells. And while this is definitely a viable way to go, there are also alternatives that should be allowed in guidelines, where one would have adequate measurement method, and they could apply parametric statistics to the population and still be able to make adequate and viable inferences regarding the distribution of the product. And, in fact, if that's the case, then the numbers that were presented to the Committee this morning would actually be smaller, and the blood center could then have a lower burden as far as sampling and ongoing process monitoring.

So, I think those are all the comments I have.

Thank you very much.

DR. HOLLINGER: Thank you.

Dr. Katz?

DR. KATZ: Probably this is one I should read the boiler plate in the AABB statements, only to point out that of the blood banking organizations, AABB is certainly the most diverse, and I think that that should be understood from the comments I'm going to make.

The AABB appreciates this opportunity to provide comments to BPAC. Universal leukoreduction of blood components is a very controversial issue for our membership, a diverse group, representing not only blood collection facilities, but hospital transfusion services and individuals and clinicians involved in transfusion medicine.

The Committee should be aware that there is substantial divergence of very well informed opinion on the propriety of FDA mandating universal leukoreduction. This is based on the perception, after extensive review of the scientific evidence, that there is inadequate scientific proof that the benefit will be worth the cost; a cost to the entire population of transfusion recipients. Viewed in this light, there are many in AABB who consider the choice of components to be the practice of medicine and, in some sense then, beyond the purview of FDA.

Others agree that a preponderance of evidence supports the benefit of universal leukoreduction, even if that evidence represents diverse studies, often with

conflicting results.

In the end, we believe that opposition to universal leukoreduction is rooted in economic concerns. If additional costs, in times of contracting reimbursement were not involved, opposition would likely be much more muted. We are aware that FDA and its advisory committees are charged to evaluate safety, efficacy and purity, and that strictly economic arguments are beyond their charge.

Against this background--if, as we perceive--FDA is not planning to reconsider the medical merits of universal leukoreduction, we would ask for two things: first, that formal guidance and regulation for implementation be expedited, so that blood collection facilities and hospital transfusion services they serve will have time lines allowing proper planning and budgeting; and second, that FDA, in cooperation with Blood Safety and Availability Committee and HCFA be explicit about the medical benefits of universal leukoreduction, so that the adjustments in reimbursement required to support this effort are in place before implementation is mandated.

Thank you.

DR. HOLLINGER: Thank you.

Is there anyone--yes, please. Dr. Sayers?

DR. SAYERS: Blaine, thanks.

I've come back here and I've taken off my ABC hat

and just speaking as a blood banker.

We've heard of all the potential benefits for transfusion recipients, in terms of universal leukoreduction, but I would like a word of caution to be added to the record concerning what happens at the donor end when universal leukoreduction becomes mandated.

This is going to be an intervention which might well be in place well before we understand all the various circumstances which influence whether universal leukoreduction is consistently effective or not. And, in particular, I'm referring to how universal leukoreduction is going to be managed by those blood programs which have a significant percentage of their donor population that are African American. Something like 6 to 8 percent of African Americans are sickle trait-positive, and we know there is overwhelming evidence that these units either do not filter, they filter inconsistently, or they appear to filter but on quality control analysis, do not, apparently, have their leukocytes removed.

This is an important donor issue. It superimposes an obligatory deferral of another group of donors against the background of an already compromised national inventory. For those blood programs that have a significant of African American donors--and, for some of them, it is upwards of 50 percent--the local blood supply is going to be dramatically

compromised.

And also, universal leukoreduction, at least as far as the African American population is concerned, will be a deterrent to identifying exactly those rare donors that are required for the maintenance of patients who are in sickle cell transfusion programs, and also those individuals who are needing marrow transplants against a background of difficulties in identifying individuals of similar ethnicity who might have compatible marrows.

So these comments aren't in any way meant to detract from the value of universal leukoreduction for certain patients, but just a caution that the effect on the donor population has also to be taken into account.

DR. HOLLINGER: Thank you, Merlyn.

Yes--Kay Gregory?

DR. GREGORY: Thank you, Blaine.

I'd like to say just a few words on behalf of a group that you have not heard from before in this particular committee, and that's a group that is known as the Coalition for Blood Safety. This is a group that is comprised of the American Association, including the American Red Cross and the Department of Defense, ABC--America's Blood Centers--and the American Blood Resource Association--or ABRA.

This group was formed explicitly at the request of the FDA to work originally on what was known as regulatory

reform, and we decided perhaps it would be better to change our name and be a little broader.

I'd like to comment specifically on the licensing provisions that Dr. Lee spoke about, primarily because I believe this may be the first time that we've heard them say that whatever they're going to do will not necessarily be a prior approval supplement. And we think that's definitely a step forward.

Since we hadn't heard the proposal before, we can't comment any more specifically, but it does appear that this is a step in the right direction, and we will be looking at the proposal carefully when it comes out.

DR. HOLLINGER: Thank you.

Yes, please. State your name and association.

DR. GAMMOND: Rich Gammond, South Florida Blood Banks. I just have a couple brief comments here.

One, at our blood bank we feel that leukocyte reduced products are medically superior products and should be considered a standard of care. In that regard, we would be in support of an FDA document requiring universal leukocyte reduction, and we also want to emphasize that reimbursement issues do need to be addressed.

Thank you.

DR. HOLLINGER: Anyone else?

So we're going to close the public hearing for

right now, and we'll open it up to Committee members for discussion.

OPEN COMMITTEE DISCUSSION

DR. HOLLINGER: Yes--Dr. Simon?

DR. SIMON: I think--I'd just like to make sure I understand correctly--from Dr. Lee's presentation, it would appear that as of this point, FDA is saying that they are not--I don't know what the right term is--they have not determined that they are going to do any rulemaking to require universal leukoreduction, but rather, I would use the term "let it happen"--all the medical community to move in that direction, and in the interim, sort of tighten up the quality control issues, and maybe loosen up, or at least facilitate the licensing issues.

Is that a correct interpretation?

DR. EPSTEIN: Not exactly. What Dr. Lee has said is that the proposed guidance document would not contain an explicit recommendation for universal or routine leukoreduction. However, it remains FDA's current thinking that we would move forward with appropriate rulemaking. The only scenario in which that might be unnecessary, is if universal or routine leukoreduction becomes a voluntary industry standard; FDA could make a determination on that basis, that it's now current good manufacturing practice, and regard it as enforceable under existing GMP regulations.

But if it remains the case that only a part of the industry adopts it, and not the predominance of the industry, then we would not be able to make that determination, as GMP.

So, what you're hearing is that we still think that it is an advancement in the safety and the purity of the products. We are seeking to facilitate centers' ability to implement now voluntarily, both by clarifying the quality control standard expected by the FDA For products bearing those labels as leukoreduced, and by facilitating the approvals mechanism. We will be encouraging voluntary implementation by recommending that it be performed whenever feasible, recognizing that there are implementation concerns.

So, over time, one of two things will happen, and I don't know which will be first. Either there will be a continued industry voluntary implementation, and we may determine that it's enforceable as a product standard under GMP, or we will, in the end create a regulatory requirement through rulemaking. But that's not a rapid process.

So the bottom line in what I'm saying is, that for legal reasons we do not believe that we can simply create a mandate through guidance. As you know, guidance, in its own right, is not binding on the industry or the Agency. Guidance is guidance; it expresses current thinking and

interpretations and expectations of the Agency with regard to existing regulation.

So, we think we can continue to make progress in guidance. We certainly are expressing the view that we consider leukoreduced products to be superior from the standpoints of purity and safety. We're seeking to facilitate continued expanded use of routine leukoreduction, but that process, in and of itself will not create a requirement. But we remain committed to developing such a requirement.

Is that clear enough?

DR. HOLLINGER: Dr. Schmidt?

DR. SCHMIDT: A couple of comments, and then sort of a question.

The disadvantages of leukoreduction listed did not include the reduction in potency. If up to 85 percent of the red cells can be lost, that means that--

DR. HOLLINGER: Not up to 85 percent can be lost.

DR. SCHMIDT: I'm sorry--if only up to 15 percent can be lost, that means that 15 percent of the blood, potentially down the drain, and the patient who would ordinarily have six exposures in transfusion to red cells would have seven exposures.

Another comment on Dr. Lee's excellent analysis is that there is something--quite a few things built on the

blood center that collects 400 units a month, and I think that's totally unrealistic. I would guess there are not very many blood centers that only collect 5,000 a year at the present time.

But a larger comment is this: When we're talking about the industry, I'm not quite sure if that needs a definition, but there are the people who collect blood, and the people who transfuse blood, and since the FDA has requirements for the transfusers, I presume they're part of the industry.

Now, the statements by the Red Cross and American Blood Centers, who are the blood collectors, always sort of remind me of architects. Architects win prizes, but they win them at the expense of their clients. It doesn't cost the architect anything to do this wonderful building and design it, because somebody else pays for it. And when we get into the other part of what I think you consider the industry, for which Dr. Katz has mentioned, doesn't the regulation--doesn't the attitude of the FDA have something to do with that medical transfusion end, which is not just concerned with the manufacturing, but the usage.

DR. HOLLINGER: Yes--one of the architects are going to--

[Laughter.]

DR. EPSTEIN: Well, yes, you're right, Paul, but,

you know, you're talking about who pays the cost, and, as you know, the FDA makes product decisions related to safety and efficacy independent of cost. That's why we separated the cost issue from the deliberations in September '98. We feel that, you know, given a nearly unanimous recommendation of the Committee--13 in favor, three abstentions--that the benefits outweighed the risks of universal leukoreduction; that independent of cost there was a fairly clear consensus.

Now, recognized, however, that cost was a daunting implementation issue, and that's the real reason that we've not moved forward more quickly. You know, everyone is asking us: "Please consider the reimbursement issue before you create any requirements." Well, that's what we've been doing. It's just that we can't do it directly as FDA. We have partners in the Public Health Service. We brought the issue to the attention of the Department has been working with Health Care Financing Administration. Progress was made in creating a new fee structure for the unit administered in the out-patient setting. The problem is that Health Care Financing Administration is fearful that if they start making DRG exceptions for in-patient reimbursement, that there will just be, you know, a watershed of requests for exemption.

And it's the current view of HCFA--and, I guess, shared by the Department--that if that part of it is to be

fixed directly, through regulation, that there should be some sentiment expressed by the Congress about creating that exemption.

So that's kind of where the issue is.

Now, what we see is that now that there has been a fee schedule established for the out-patient unit, it is at least possible for blood centers to argue to hospitals--and I would hope successfully--that the real cost of providing an in-patient unit is no less. Because the argument that HCFA has made repeatedly is that the problem is not lack of funds; it's that the hospitals, which HCFA believes receive adequate funds, simply are not electing to spend them on the blood unit. In other words, they're not accepting that that's the cost of what a filtered unit, or a NAT-screened unit really is.

So we think that not all these problems belong to the FDA to be solved; that there is more advocacy needed directly with HCFA, and potentially even with Congress.

Where FDA stands is, that we understand that the cost issue needs to be resolved before you could comply with a mandate. We also have the problem that our attorneys tell us, that even if we were to make a recommendation, but put some future date of implementation, that that would also have the force of rulemaking through guidance, and we shouldn't do that.

This is different than other issues, because the current products are defined in the regulations, and the notion is that if we somehow make obsolete the products defined in the regulations, aren't we doing rulemaking through guidance? And, of course, under the Administrative Procedures Act, we can't do rulemaking solely through guidance.

So we simply have the convergence of the legal constrains on how far FDA can go in guidance; the problem that, you know, reimbursement won't be solved by FDA, but needs to be solved; and then the issue of time-frame for creating a regulatory requirement. And so we're simply moving, you know--lurching forward at an uneven pace on these three fronts.

But we are moving on all three fronts, and I think that that's the major take-home message; that FDA remains convinced at a scientific level, independent of cost, that universal leukoreduction is a general improvement in product purity and safety for the non-leukocyte-dependent products. We remain committed to facilitating the expanded use of leukoreduction on a voluntary level, and have taken the actions that Dr. Lee--or the pending actions that Dr. Lee has described, and we are cooperating with the Department and other health care agencies to see if the reimbursement problem can't be solved within a reasonable implementation

time-frame.

And I would suggest that progress is being made on all three fronts. It's just that everybody is trying to envision the end-point, and everybody recognizes we're not there yet. And that's true. But it's not for lack of awareness that these things play off against each other.

And I have to say that I think one of the difficulties has been that a large number of very highly respected experts in the field of transfusion medicine have either written to the FDA or published articles, or made public statements, in opposition to universal leukoreduction on scientific grounds. And yet there's the nagging concern that many of the same people are the ones who are in the economic bind. And the thing that's unclear is: what would they be saying if there weren't the same economic issue?

And so I think it's quite significant, what we heard from Dr. Katz, that it's at least the view of the AABB, as an umbrella organization, that if the cost issues could be put aside, many of the arguments that we are hearing would be greatly muted. And, you know, again this is one of the numerous factors that we have to deal with. We understand that people can't ignore the cost problem, but the extent to which it's coloring the scientific arguments--or purported scientific arguments--is confusing.

Again, when we brought the question, independent

of cost to, you know, a dispassionate, non-conflicted committee, we got a very clear answer. And I'm not sure that it was a wrong answer. I don't believe that it was.

And I can tell you that in private conversation, even some of the signatories of the published letters decrying requirements for universal leukoreduction have stated to me that if the reimbursement problem were solved, you know, that wouldn't be their position; they'd do it in a flash.

So, you know, I mean, I guess that that's anecdote and it's, you know, sort of not evidence, but it does tend to convince me that we have at least muddied the debate. But the bottom line is that the FDA is not seeking to impose this in any way that could not be implemented at a practical level.

DR. HOLLINGER: Yes, Dr. Linden, and then I'll come back to the military.

DR. LINDEN: I'm concerned about the quality control procedures that you're talking about, and I'm hoping someone from the Agency can comment further, as they would apply to small facilities.

Dr. Lee talked about "small centers," and Dr. Schmidt, you know, mentioned "blood centers," but, in fact, a significant amount of blood is collected by hospitals--it's over 10 percent in New York State.

And it seems that if there is a burden, that hospitals collecting only a few thousand, perhaps even a few hundred, units had to quality control a significant portion, or perhaps even all of their units, versus a large blood center that might do a tiny, tiny fraction, there is really going to be a burden that would be a tremendous disincentive for those hospitals to collect their own blood.

So I'm--I guess I'm concerned about this approach to the quality control. And we did hear from one of the public commenters that there might be other approaches, so I'm just wondering about the Agency's thoughts on this issue.

DR. LEE: Yes, that's quite true. And we have thought carefully about how we might impose only an equivalent burden on small centers--hospitals--and still come away with the same level of assurance that your process is in control. And we haven't really been able to come up with a solution any better than what I just presented this morning.

One approach might be to reduce the QC burden based on track record. Even though initially you might go with a fairly high burden of QC testing if, over time--say, a period of two years or so--that it's clear that your process remains under control, perhaps that level can be diminished. And from a statistical rigorous standpoint, I'm

not sure exactly how that can be justified, but that's to be further debated. But I think there is room for using track record as evidence for perhaps diminishing the burden.

DR. HOLLINGER: John?

DR. BOYLE: Just a question on the same issue, and that is: I was sort of surprised by your sample sizes for the small facilities. It didn't look like you were using a finite-population correction factor in the selection of those sample sizes.

DR. LEE: Actually, I have.

DR. BOYLE: You have?

DR. LEE: Yes--the initial chart, where I pointed out the confidence level and the sensitivity, that did not, and that was just to illustrate a point. But the subsequent chart of 60 units as the upper limit for large centers making 250 units or more, and then the numbers that are smaller, for centers that are making a smaller amount of units, those numbers have been adjusted for that.

DR. BOYLE: Well, what I don't understand is, with the smallest unit you're basically requiring the full population.

DR. LEE: Right.

DR. BOYLE: The question is: why? Because a sample is a sample. You don't need the full population to be able to detect the level that you're talking about,

unless I didn't read this stuff correctly--which is possible. But it seems like you should be looking at--there seems to be ways around those smaller centers--there's no reason why you have to do 100 percent quality control to be able to identify a process failure.

DR. LEE: That goes with the number of signals that you're going to get. I mean, if you're making only, say--let's say you're making 20 units. That's all you're making. That means if you operate very close to the process requirement of more than 95 percent units being acceptable, then that means you're going to only have one unit. The chances of you picking up that one unit alone, it's pretty slim, unless you test every one of them. That remains a problem.

DR. HOLLINGER: Yes, Dr. Linden.

DR. LINDEN: Yes, if I could just ask a follow-up question: you're talking about lowering the acceptable limit--right?--to 1 x 1.0 x 106 instead of 5x1.0 x 106?

So--and I think that's largely because it's achievable, more so than the scientific data have shown that that's absolutely necessary--at least we haven't seen those data today, at least--

DR. LEE: Yes, it's--

DR. LINDEN: --to know where that figure came from.

So, couldn't there be some flexibility? I mean 5x1.0 x 106 has been okay all this time.

DR. HOLLINGER: The Europeans use one--less that 1x1.0 x 106.

DR. LEE: That's true. I mean, I don't know, from a medical standpoint, what 1 versus 5 means, in terms of the benefits that you derive from increased product purity.

We can remain at 5x1.0 x 106, but the Europeans have gone forward with 1.0, and there is no reason for not doing that, because that's readily achievable.

DR. LINDEN: Right--yes, I mean, I'm not saying that I don't think 1x1.0 x 106 is appropriate, I'm just suggesting that there may be, I guess, a gradation of ones that are close that--I mean, clearly you need to detect ones that are unsatisfactory and that there's a real problem in your system. But if you have only minor deviations, so that, well, maybe one comes out to be 2x1.0 x 106, that may not be quite such a concern. And this has, again, to do with sample size, and what type of deviations you're going to be picking up.

DR. LEE: So you're referring back to the quality control burden.

DR. LINDEN: Yes, yes.

DR. LEE: For instance, if you picked up an unacceptable unit, but that's between 1 and 5--

DR. LINDEN: Exactly.

DR. LEE: --then you might kind of--I see. That's another approach to perhaps diminishing the quality control burden.

DR. LINDEN: Yes, I may not have been clear with--yes, that's what I meant.

DR. LEE: I see.

DR. HOLLINGER: Yes--Marion. Dr. Koerper?

DR. KOERPER: Just a point of clarification with all of your calculations.

If you're talking about a center producing 400 units, are you talking about 400 units a month, or 400 units a year?

DR. LEE: That ties in with the concept of manufacturing period.

DR. KOERPER: Exactly.

DR. LEE: The current recommendations--the 1996 memorandum--that are currently in effect today, that goes on a monthly basis; number of units per month. So four units per month, or 1 percent of the units produced in that month.

DR. KOERPER: No, what I'm going by is--you were saying if a center produces more than 250 units, they only have to test 60 units.

DR. LEE: Right.

DR. KOERPER: Is that "more than 250 units" a

month or a year?

DR. LEE: And as I've described this morning, I left some room for facility-specific decision. You can define it as a month if you choose to, but you can define it as three months, if that will suit your QC burden better. But it cannot be any longer than a month. There has to be some--

DR. KOERPER: It can't be longer than three months.

DR. LEE: I'm sorry--any longer than three months, because there has to be an upper limit.

DR. KOERPER: Right. Exactly.

DR. LEE: If there is no upper limit, well you might say, "I look at it every year."

DR. KOERPER: Right. That was the point I was trying to pull out, because that was what I was having difficulty with.

So, a center could say, "We produce 250 units a month--in three months--"--

DR. LEE: Right.

DR. KOERPER: --"--therefore we only have to test 60."

DR. LEE: In that three-month period.

DR. KOERPER: In the three-month period.

DR. LEE: Right. Of course a disadvantage of that

is that you are question-mark for that three-month period. Until you close the loop of all of you're testing, you're not exactly sure that you are at the 95 percent--

DR. KOERPER: Right.

DR. LEE: --confidence level.

DR. KOERPER: But on the other hand, you have to test at least one unit a week.

DR. LEE: Right.

DR. KOERPER: So--

DR. LEE: That allows you to detect an unacceptable process earlier--

DR. KOERPER: Right.

DR. LEE: --but in no way does it assure an unacceptable process any earlier, until you finish--

DR. KOERPER: Right.

DR. LEE: --the entire period.

DR. KOERPER: But on the other hand, this is a continual, on-going process, because once that three months is up, then you start the next three months, so you're going to keep doing your QC every week.

DR. LEE: That's correct, but--

DR. KOERPER: And--

DR. LEE: --it's a matter of product retrieval--

DR. KOERPER: --it's a moving target.

DR. LEE: --it's a matter of product retrieval and

constancy notification. When you discover an unstable process, what are the units that are expected by that unstable process? If you define your period short, then you have less products to worry about.

DR. KOERPER: Right.

DR. LEE: If you define it with a long period, then you have more products to worry about.

DR. KOERPER: But if you want to be totally sure, then you would have to test every unit.

DR. LEE: That's correct.

DR. KOERPER: So I think that you have to compromise with what's reasonable for the blood banks to do. And I'm thinking specifically of the hospital transfusion services -- DR. LEE: RIght.

DR. KOERPER: --that are not collecting as huge a number. If they can at least aggregate over three months--

DR. LEE: Right.

DR. KOERPER: --then that might lessen their QC burden somewhat.

DR. LEE: Right. And at this point, we think that should be an option for small centers--right.

DR. HOLLINGER: Dr. Fitzpatrick?

COL. FITZPATRICK: May I expand on Dr. Schmidt's comment for a minute, and ask the FDA to re-think it's 85 percent recovery level?

DR. LEE: Yes, I was trying to come back to that. Go ahead, I don't want to--

COL. FITZPATRICK: If I could do an illustration here: if we collect a unit at the top end of the scale--at 495 ml, with a 38 percent crit, and recover 85 percent, we're recovering approximately 160 mls of red cells. If you recover 80 percent, you're recovering 150 mls of red cells, but that's unacceptable. And if you collect a unit of the low end of the scale--at 405, at a 38 percent crit, you're recovering at 85 per cent 130 mls of red cells, but that's an acceptable unit.

DR. LEE: Right.

COL. FITZPATRICK: And that's a disparity.

I would encourage the FDA to act on other comments that I know they've received from other people to determine a minimum effective therapeutic does of red cells, and establish that at 150 ml, 130 ml, or a grams of hemoglobin, and do away with the recovery thought process that is fraught with error anyway in many centers when you try and determine recoveries, because there's--depending on your method, there are difficulties in doing that.

And I think it would simplify the process a great deal.

DR. LEE: Thank you for the comment.

COL. FITZPATRICK: And then just another, I wanted

to support Dr. Sayers in his comment on sickle trait, and perhaps other hemoglobinopathies. I think that is a potential problem for many of us, dependent on our donor population, and that prior to this becoming either a standard of care or a mandated requirement, we need to be able to deal with those donors and utilize them as either non-leukoreduced or leukoreduced products if an acceptable method becomes available.

DR. HOLLINGER: Yes, Dr. Ohene-Frempong?

DR. OHENE-FREMPONG: Yes, I just wanted to react to the last comment, about the sickle-cell trait donors.

Our sickle cell center, which I direct in Philadelphia, probably has the largest chronic transfusion program in the country. We also, in addition, have a very aggressive partnership program with our local--regional American Red Cross center to increase African American donors, specifically for our sickle cell disease patients.

We--because we don't use sickle-cell trait blood for donations for sickle-cell disease patients, all the African American donors are--their blood, at least, is screened for sickle-cell trait. So we know very well the percentage of the donors who have sickle-cell trait.

I just stepped out to check with the blood center. They have adopted universal leukoreduction now for a couple of years, and they tell me that they have not, up to this

point, even though they've heard about it, they have never had to reject any units because of sickle-cell trait filtration. So whatever the technical differences may be in different laboratories in the past, it's worth checking. But I just checked with them, and they're collecting several thousand units from African American donors, and the fat that somewhere around 8 percent of them also may have sickle-cell trait has not been a problem.

DR. HOLLINGER: Thank you.

Yes, go ahead, Dr. McCurdy.

DR. McCURDY: There have been several comments about the potential loss of cells--red cells or platelets--when you filter those. The Institute--NHLBI--supported two studies looking at some of the effects of leukoreduction. One of them was the TRAP study trial to prevent alloimmunization to platelets, and the other one was the VAT study--viral activation by transfusion.

In both of those studies, they looked very carefully at the--how many units of red cells or platelets were given to these recipients, both leukodepleted arm and non-leukodepleted arm, and there was no difference. So that regardless of how much you use, this doesn't apparently filter through--if you'll pardon--filter through to the clinicians who actually order the transfusions. They still

give approximately the same number of units, whether they're leuko-filtered or not.

DR. SCHMIDT: I think the usual surgeon still thinks he's giving a pint of blood every time he gives a unit of red cells--

[Laughter.]

DR. SCHMIDT: --and he calculates that out in the quantity of fluids lost and replaced.

DR. McCURDY: These were all medical patients. The VAT trial used patients with end-stage AIDS who required transfusion, and the TRAPs trial used primarily acute granulocytic leukemia patients. So they weren't surgeons. They were hematologists, oncologists.

DR. LEE: If I could just add a comment. For red cells, the recovery--although I've stated 85 percent recovery--for red cells, the recovery is far higher than that. In fact, it's close to 99 percent.

For platelets, there is probably more of a loss, but it's still well below 15 percent.

DR. McCURDY: Blaine, I have one more comment. The suggestion was made that we define a unit of red cells as to how many ml of red cells, or something along that line.

And that might be a reasonable thing to do. On the other hand, there have been a number of people who have

made an attempt to define the transfusion trigger--that is, at what stage should you give a unit of red cells, of whatever size, and that's proved to be a very, very formidable task. Nobody has been able to do the kind of study that would clearly define at what stage should you transfuse a patient with red cells.

DR. LEE: That question, of course goes--oh, I'm sorry. I'm speaking out of turn.

That question goes, of course, beyond the problem of leukocyte reduced. It's just about blood, in general. And we could address it, at least in part, through leukocyte reduction by defining the actual red cell content, or therapeutic cell content rather than recovery. That's an option that we could go, as a partial solution to the bigger problem.

COL. FITZPATRICK: I'm not suggesting that we standardize a unit of red cells and say "every unit is going to be 250 ml," but let's set a floor--a minimum level, knowing that there's going to be a range above that.

DR. LEE: Yes, with respect to leukocyte reduction, we could do that. For instance, you could simply take the weight and the hematocrit or platelet count of a post-filtered unit, and establish a minimum standard for that. That's one alternative--one of many things that weren't particularly referred to in my talk.

DR. HOLLINGER: Dr. Lee, is the process--the pre-storage leukoreduction, is that technician-dependent at all, or is it device dependent, so that if you have technicians who are doing this, and they change, that one would--because it gets back to sort of what Jean was saying about quality control. Is it--therefore is it facility-dependent and device-dependent more than technician-dependent?

DR. LEE: I'm afraid it is--

DR. HOLLINGER: Afraid what is?

DR. LEE: Technician-dependent.

DR. HOLLINGER: It's technician-dependent.

DR. LEE: Yes.

DR. HOLLINGER: Which means that if the technician changes--if you get a new technician in that's doing it, then that person needs to be validated in doing the procedure then.

DR. LEE: That's part of training.

DR. HOLLINGER: Yes.

DR. LEE: Staff training.

DR. HOLLINGER: Ah--yes, Dr. Katz? You had a comment.

DR. KATZ: I just wanted to give some data perspective on the sickle cell issue. What's being seen at centers that are looking at the problem now is that,

depending on a variety of circumstances, as many of 50 percent of sickle trait units will not go through a filter, which is less problematic than the fact that those that do go through the filter are not adequately leukoreduced.

We have no substantial data across the filter manufacturers. We have no substantial data across multiple centers. And so it's an issue that's being looked, and hopefully in time for the fall meeting so that we have a clue.

It doesn't surprise me that the Red Cross might not have recognized the problem. The real issue is the units that go through the filter, and when you count them, they've just got white cells in them.

DR. HOLLINGER: And when you find -- when you do quality control, and you find something that is a problem--a validation--not a validation problem, but a problem in the quality control, what do you do about the units that are--I mean, do you assume that only units that occur after that are going to be a problem, in terms of filtration? Do you assume that units which are already in the facility haven't been used are a problem then, and do you do something about those--or what?

DR. LEE: Well, that again sort of ties back into the concept of the manufacturing period. The way we envision that working right now is that if you complete your

manufacturing period, and complete your full amount of QC testing that we require for that period, you've closed that period off, and you're okay.

Let's say you discover an unacceptable unit at some point in the middle of a period. Then all units manufactured since that period is subject to some question. So for those units, you will have to either directly test them, and re-label them properly--you'll have to first find out what the process error is, and if you're able to narrow down the units that are affected by the identified process error, you may minimize the number of units that you have to directly test.

DR. HOLLINGER: And should you change testing and QC based upon getting a new lot--on the basis of a new lot that comes in from a manufacturer or not?

DR. LEE: Right now there are no lot release requirements. It's accepted for filters to perform in an equivalent fashion, and if a lot problem does creep in, that can only be detected through the quality monitoring process . Hopefully, as a part of process investigation you will be able to narrow your problem down to the lot. But right now, after your initial validation of your process, you're strictly relying on your quality control monitoring on an ongoing basis to detect any problem in the lot.

DR. HOLLINGER: Because I would think that despite

the fact that there are lot releases, and so on, that are required, it's been my experienced, at least with things--that you should probably test each new lot that your getting out, at least in some respects, and not just--unless you have a weekly frequency of doing things.

DR. LEE: Well, with respect to lot-release testing, if lot-release testing is to be performed, it should probably be performed by the filter manufacturer, and not--under current 510(k) clearance mechanism lot release is not required.

DR. HOLLINGER: Okay. Thank you.

Dr. Chamberland?

DR. CHAMBERLAND: That raises the question--and I'm not sure if FDA is planning to include this in its guidance document, but what do you do with those units who fail the filtration process, either up front--meaning, as we've heard, some units just don't go through a filter--or, let's say in the middle of your three-month manufacturing period, or at the end of it, you discover that you have had some QA problem and, in fact, in your inventory there are, indeed, units that would not meet the required white blood cell reduction level.

In this time of inventory shortages and whatever--and let's say we move into an arena where, essentially, it's require to have leukocyte reduced

products, would there be a role for the use of non-leukocyte reduced if they were so labeled?

DR. LEE: Sure. Non-leukocyte reduced products will continue to be available, and you can do one of three things on the discovery of an unacceptable process, and hopefully you are able to identify the number of units that were potentially affected by the unacceptable process.

Either those units have been released to consignees and have been transfused, in which the consignee notification is all we can do; they have been released to the consignee and remain under the control of the consignee and have not yet be transfused, in which case you can ask them to send them back; and, thirdly, the units are still in the control of the blood center, in which case you should directly test them. And it's possible to label them as not-leukocyte reduced--simply label them as just regular blood, because it failed QC testing.

DR. CHAMBERLAND: So FDA envisions that even if we carry this to sort of the regulatory step of this--a requirement for leukocyte filtration, FDA still envisions that there still would be use, on a day-to-day basis of non-leukocyte reduced units.

DR. LEE: I think that product should still be available for physician choice.

DR. CHAMBERLAND: Okay. Because I was going to

ask--well, then the next question I had in my mind is, practically speaking, will there really be--except for these instances through QA failures or whatever--really be out there available non-leukocyte reduced product if the physician chooses to order such. I mean, those of us who sit at the Advisory Committee on Blood Safety and Availability heard testimony from a blood bank director that he was, essentially, at this stage being forced into accepting leukocyte reduced product, because that really was all that his source was sending him. I think there was some sense of the concern stemming from some economic considerations, that he wasn't going to get--his hospital wasn't able or willing to pay for this, and he didn't feel, at this point in time, that he needed a hundred percent inventory of leukocyte reduced product.

So I'm just wondering, again, if you carry this out down the road to its natural end--it sounds like the Red Cross, for example, isn't really going to have non-leukocyte reduced product available, unless it's through a QA failure or something like that. So I'm--

DR. HOLLINGER: Yes, Dr. Macik?

DR. MACIK: And actually that was kind of some of the points that I wanted to get to, and these are more just comments, being a treater--clinician--predominantly and not a blood banker.

You know, until this issue came up recently, leukocyte reduced has not been a big focus issue outside of this arena--or blood banking arena--as far as the general clinician out there. And I think if you would go out and ask family medicine and various others, you know, "What about leukocyte reduced? Are you going to be in support or against this?" I don't think they would know what you were talking about. And who orders the unit of blood? The unit of blood is not ordered by the blood banker, it is ordered by the physician who is treating a patient.

And so I think there's been a lack of education across the board, and instead--and I don't think it's entirely inappropriate that the people making the decision to use this or not use this, or to implement this or not implement this are--quote--"experts in the field." But I think it's kind of being forced on the users without their really even knowing it's coming. They, however, do feel the impact--the financial burden--and there is absolutely no way you can separate out the financial component of this, even if you're going to say we're going to do it on scientific method.

You know, I don't--there's just no way that you can separate those two issues. And I know that we've been told that we're working on three fronts and we're going to try to cover that.

So the concern I have is if--you know, what is the routine physician out there ordering? Are we going to be put in a position which was brought up and has been hitting some of the press, that the decision is already going to be made, because the only thing you're going to get is leukocyte reduced when you order 15 percent leukocyte reduced and they send you 50 percent, you're going to have transfuse that blood, and you're going to wind up being caught in a bind about how are you going to pay for that blood, and how are you going to get people appropriately treated.

So, I have great concerns about how things are moving forward, and what's happening, and what's really available out there.

I don't--I am for the purest product possible, but I also don't trust processes that supposedly help to reimburse this, and I can see great problems coming along. Speaking just from the hemophilia standpoint, you know we all know there's a best product out there, and yet now facing government funding that says "We're not going to allow you to get the best product, because we're only going to give you enough money to buy the second-best product." And if we have that on a small front, how do we know we're going to get covered in this big front, to provide the best product?

And I was not privy to all of the information, you know, about why this is so clinically important, and so much clinically better. You know, I have to just take--we weren't presented any of that information, because that was in the, you know, previous Blood Products Advisory Committees. But, you know, I think there's a lot of information out there I feel like I don't know--being part of the Committee now--that I've inherited from past Committees, saying that this is obviously the best thing to go forward with.

So--long-winded, but just some comments to make on being a clinician and, you know, what kinds of things are happening here.

DR. HOLLINGER: Yes--Dr. Simon?

DR. SIMON: Kind of coming back to the beginning--because I think we've kind of gone around. And with Dr. Chamberland's comments, there seemed to be answer from FDA: yes, there would be leukocyte reduced blood available. Well, I guess there is during the implementation phase, but this time I think I did understand the FDA position correctly, which is that at some point all red cells, platelets--and now they've mentioned plasma as well--would be leukoreduced, and that would be the only component available to the clinician. It won't be tomorrow or the next day, but at some point, if not by rulemaking, by

practice.

DR. HOLLINGER: I wasn't real sure why--did they really say the plasma also? I mean, with its less than 1x1.0 x 106--

DR. SIMON: I wrote that down. Yes.

DR. HOLLINGER: I mean, that would be kind of unusual, if--to me it seems a little unusual, if you're going to require red cells to be only less than 1x1.0 x 106, and my understanding is most plasma units are 1x104 or less for--

DR. LEE: Yes, that's absolutely correct. And, initially, the Agency felt that there is no need to specially consider plasma components for leukocyte reduction.

However, I think there is several groups that are concerned about being able to label a plasma unit as leukocyte reduced; again, sort of pressure from international discussion of this topic, where other countries are recognizing plasma, leukocyte reduced. And in order to sort of interact with them, we have to demonstrate--U.S. products have to be able to be demonstrated as the same as the ones that are labeled as leukocyte reduced in other countries. That's part of the reason.

And also, manufacturing failures do occur. If you

were to manufacture a plasma product in accordance with GMP, you should arrive at a product that's well below the leukocyte reduction threshold already. However failures do occur. You might consider them just as failures and treat that separately as a failure case. But you might also consider, well, if you want to demonstrate that plasma, if it is indeed leukocyte reduced--as we assume--you might also perform QC testing on them too, to ensure that some kind of a GMP failure hasn't occurred.

So it's possible to recognize products--plasma leukocyte reduced--based on the fact that if you perform the appropriate QC testing as you would for other components that you can label it as such, but the method of getting there is no more burdensome than what you're using anyway for manufacturing plasma. All you have to do is QC a few of them to make sure that you're under control You don't have to filter them. We certainly don't want to encourage the extra use of filters just to filter plasma through, because it's not necessary.

DR. HOLLINGER: I think that's what--I mean, that's what my understanding was, that it's not necessary to filter them--

DR. SIMON: It wouldn't be necessary to filter, but I assume that you would want some kind of quality control program to make sure that you're meeting that

standard, if that's the case. Is that correct?

DR. LEE: That's sort of the current thinking, that you would subject these plasma units that are manufactured under routine procedures, not using a special leukocyte reduction step, but simply subject them to the QC testing process, and demonstrate that you're in control for leukocyte reduction standards.

DR. HOLLINGER: Yes?

DR. EPSTEIN: Yes, I agree fully with what Dr. Lee has said.

I wanted to come back to a different point about sickle trait. There are documented problems with leuko-filtration in the face of sickle trait, as Dr. Katz said, and also the experience in Europe. But the idea that you have to routinely reject the donor may not be well-founded, because you can still prepare leukoreduced platelet and plasma by apheresing the face of sickle trait, and also those donors may still be suitable for collection of peripheral blood stem cells by apheresis.

So I don't think one has to think solely in terms of filtration--that's my only point. Filtration is not the only method of leukoreduction, although there's a recognized problem with filtration in such persons.

DR. LEE: If I might just add a comment to that topic.

One way to get at this would be just to screen red cell donors up front. But there's no current thinking, at this point, to require such sickle cell screening for leukocyte reduction process. Typically, though, I think a sickle train donor will become apparent during the filtration step. I think we've heard something like 65 percent of them will just not filter, and you'll--it's apparent that this is a filtration process failure--right there--and you'll be able to recognize that product.

For the few units that do go through, I think the time that it takes for that filtration to complete is variable, but it's going to be far in excess of the typical filtration time. So what you might choose to do is specify a certain time limit within which the leukocyte reduction filtration process must be started and completed. And typically a unit will filter easily within 15 minutes or less. In some cases, the filtration might be completed within half an hour without any particular reason for that, but in almost all cases, I think you will find that sickle cell donor will exceed those typical time limits and you'll be able to identify those units there.

So although you won't prevent the donation from happening--and the filtration from happening--you'll be able to retrieve the unit in advance of actually picking up them up through random quality control testing.

DR. HOLLINGER: Yes--Dr. McCurdy?

DR. McCURDY: I have some incidental intelligence that there's a representative of the American Hospital Association that hadn't planned on commenting but might be willing to. Would you reopen the public hearing for that purpose?

OPEN PUBLIC HEARING

DR. SAVER: As indicated, I had not intended to make a statement this morning--

DR. HOLLINGER: Could you--

DR. SAVER: My name is Mary Beth Saver, with the American Hospital Association. But I did want to take a couple of minutes to respond to some statements that have been made this morning.

I will tell you that we have been hearing from our members--transfusion medicine specialists within some of our major institutions--about their concerns with universal leukoreduced blood. They have no problems, and they believe wholeheartedly in the targeted use of this blood, but they do not believe that ULR is scientifically indicated. I know Dr. Epstein and others have made comments this morning, is that because of cost? Is it because of the science?

I can tell you, again, just what I'm hearing from the members that are calling me is they have definite concerns on the science, and they believe with limited

health care resources that the science should be followed.

So I just wanted to comment on that.

In addition, I know we've talked this morning a little bit about reimbursement. With $71 billion having been cut out of the hospitals by the Balanced Budget Act, contrary to what HCFA is saying, that we can cover our costs, many of our hospitals cannot. And on the reimbursement front, we are working toward two different avenues: once is a cost-securing campaign, which--two bills have been introduced. One is in the House and one is in the Senate. This is a 2.9 percent increase in the update for hospitals. The cost of blood is prominently featured in this campaign.

In addition, we are working with the blood groups--AABB, ABC, American Red Cross--to come up with, also, a separate route just for blood. And we believe that is going to culminate in legislation, hopefully, that will be .5 percent increase in the overall update for blood.

As Dr. Epstein commented, it is very difficult to target specific DRGs--it opens up the floodgates--and we believe this was a better route.

Going back to the cost-securing campaign, I can tell you that there is a lot of interest on the Hill. There are 260 House sponsors of the bill. There are 48--I believe 48 Senate sponsors, which is pretty good for the Senate.

Typically, you may get 15, 20 co-sponsors on a bill.

So, again, I just wanted to make these comments from the reimbursement side, and also what we are hearing from our members. I will tell you that what drives AHA, though, is first and foremost, is patient care and making sure we're doing the right thing for our patients. But we are hearing from our members: is this scientifically indicated?

And the last question, if I might ask--and I go back to some confusion I have had--I believe Dr. Simon brought it up--is I'm still not understanding: will leukoreduced blood, and non-leukoreduced blood be available? I know, for instance, with what the American Red Cross has been saying, they're converting all their manufacturing to leukoreduced blood. And I suppose, I guess, a hospital that's dealing with American Red Cross could purpose their blood from someone else if they want non-leukoreduced, but I guess that would just be a question I would like to pose, if that's appropriate.

And thank you very much, and I'd be please to answer any questions.

Thank you.

DR. HOLLINGER: Thank you.

Ahh - Marion.

DR. KOERPER: I just wanted to make a comment

about--first of all, I believe that we should have leukoreduced blood to the extent that it's possible, because I think our charge is the safety of the blood supply. And while the financial considerations are, of course, important, I think that--I applaud the way that this is being handled in that, simultaneously, the Blood Safety and Availability Committee has been asked to comment on this, and the bringing in of HCFA at an early stage in this, rather than waiting until it's reached a rulemaking thing and then somebody saying, "Oh, wait a minute, we better change the reimbursement structure."

So, I'm very encouraged by seeing this sort of dualistic approach of two different agencies' trying to work on this at the same time.

One comment about the requirement that it be filtered within 24 hours: talking with the director of our transfusion service at our hospital, and also at the blood centers of the Pacific--one issue is that NAT testing takes three days to get a result back. If the unit is unacceptable and has to be discarded, but has already been filtered, then there's--the blood bank has incurred an additional expense that they can also not recover, because they filtered the blood that they're not going to be able to transfuse.

So there's been some sentiment expressed that

perhaps the timing of the filtration could be long enough to allow for the results of NAT testing to come back, and the units that were deemed acceptable could then be filtered at that point. So 72 hours has been suggested as a more manageable time frame, to help with some of the cost-containment issues.

DR. HOLLINGER: Well, Marion, it's my understanding--I mean, if you just look at the numbers for HCV, now it's like 1 out of 300,000 units--our policy. So I think we're talking--and correct me if I'm wrong here--I think we're talking about pretty small numbers here.

DR. KOERPER: Oh, I agree completely. But this has been an issue that I've heard raised by at least two different blood center directors.

DR. HOLLINGER: Is there a problem--I mean, just on what Marion has just said, for the American Red Cross, or somebody speaking from one of the organizations--is 24 hours a real problem for most blood organizations?

Somebody might want to comment about that.

DR. KATZ: It's really going to depend on which specific center and system you're talking about, and how far the unit has to move, physically, from point A to point B.

I think there are some places in the Red Cross system--blood systems--where 24 hours might get pretty tight: small centers like mine, or medium-size centers like

mine, 24 is not really an issue. But I think the big systems are going to have problems, and you're really going to want to talk to the Red Cross, and blood systems in particular--perhaps New York Blood Center--to find out the real burden.

DR. HOLLINGER: Somebody from the American Red Cross? Can they just comment about that issue?

DR. CHAMBERS: I think that's correct, that the testing issues are going to be a drop in the bucket compared to just the practical issue of physically moving units that have been collected at remote sites back to a processing center, and having them hit the processing center at a time when the component laboratory is prepared to do the leukoreduction. 48 hours is operationally many fold better than 24 in that regard, so that something collected, for example, late on a Saturday could be the first thing on Monday morning collection, whereas a 24-hour limit would mandate that you be doing leukoreduction processing on Sunday.

DR. HOLLINGER: And I don't hear you saying that because somebody says it's going to be 48 hours, that everything's going to be checked at 48 hours. Probably the large majority--

DR. CHAMBERS: No--correct.

DR. HOLLINGER: == of them would be tested much

earlier than that.

DR. CHAMBERS: Testing completed and leukoreduction completed.

DR. HOLLINGER: And it would allow you to do the few that--

DR. CHAMBERS: I would encourage you to look very carefully at what is known about the point at which the cytakines kick in and the cell degeneration becomes substantial, and I think you'll be reassured that even 48 hours builds in a large margin of safety, and is well early enough in the storage period that you haven't compromised the effectiveness of the leukoreduction.

DR. LEE: There's actually three camps within the Agency as to the upper limit for leukocyte reduction. One camp is to suggest a time limit that is consistent with all filters that are already on the market, already approved. They have--each filter came in with a particular instructions for using that filter, and the time limit for using that filter. So, pick a time limit that's consistent with all the filters that are already out there--that's one suggestion. And that would put the limit at something like seven days.

The other, second, camp is to choose 72 hours--three days--and that's sort of the compromise position; recognize that operational complexity, but also

try to minimize the time period within which cell degradation and cytakine generation can be minimized.

The third camp is 24 hours. That's the most stringent one. And if you do that, it's the best product, but it obviously creates operational complexities.

So we're not decided, but certainly your comments are well taken.

DR. HOLLINGER: Dr. Lee, have we answered many of your questions? I think most of the comments have been, I think important and pertinent?

DR. LEE: Thank you very much for the very helpful insights.

DR. HOLLINGER: If that is all for today--I just wanted to ask--just a question of the Committee. Well, no, it doesn't matter. We'll discuss the time for the next meeting. The next meeting has tentatively been set for the usual time in September. I think it's the 14th and the 15th for right now. Is that a problem for anybody on the Committee?

Well, be thinking about it.

Yes--there's one person.

Okay. Anyway, I want to thank again the Committee for its deliberations today, and we'll see you in September.

Thank you.

[Whereupon, at 12:20 p.m., the meeting was

adjourned.]

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