Then, it gets into a message we are giving donors you can't donate if you have sickle cell trait, and I think that is a problem.

MS. ROSS: Sonja Ross from the Sickle Cell Disease Association of America.

The targeted screening that you were conducting on a certain population, more so because of the comments that have come out and that you were using sickledex or some sort of solubility testing, and I guess our concern has always been that there would be a uniform way of testing, and electrophoresis, for example, would be that way, and then you wouldn't miss any population.

I think we need to get away from solubility testing as the way of screening for sickle trait or for the hemoglobin disorders because it is not going to give us the proper information that you would need. C-trait is also needed. Sickle beta-thal is missed if you get someone that is sickle-positive, but you don't know if it is beta-thal. So, I mean those things are very important.

MS. JENNINGS: We are in negotiations right now for hemoglobin electrophoresis instrument and reagents because we are going to move to that.

DR. NELSON: Ron.

DR. GILCHER: Ron Gilcher, Oklahoma. Kenra Ford will be talking next, so I don't want to steal any of her thunder from our shop, but approximately 25 years ago, when I was at the University of Pittsburgh, and Central Blood Bank of Pittsburgh, we uncovered a total of 7 Caucasian donors inadvertently who were, in fact, sickle trait, and that occurred with our red cell freezing program, because when we attempted to deglycerolize them, we couldn't do that at that time.

All 7 of those donors, and that is enumerator, the n was about 70,000 individuals, so it was about 1 per 10,000. Remember, that is Pittsburgh, a very ethnic area or town, and all of those individuals were from the Mediterranean basin. There were some Sicilians, Greeks, and Italians.

That is the first comment. The second comment is that I think that sickledex screening is a valid way to screen, but then you need hemoglobin electrophoresis as confirmation, and I think what Kenra will tell you, and I hope so, is that we are doing screening on non-Caucasians, so not isolating it to one particular race.

DR. NELSON: Mary.

DR. CHAMBERLAND: I am just trying, with each of the talks that have presented data, realizing there are many different variables, just trying to get an overall sense of rates of failure and what proportion of those might be due to the sickle trait, I believe in your introduction, you stated qualitatively that you were having difficulty, that a significant proportion appeared to be due to sickle trait.

Do you have any more detailed information that you could give us, like of the number of donations that were filtered, how many failed, and of those that failed, how many were due to sickle trait?

If it is in your charts, I apologize, I can't read it, because when they xeroxed, your background blacked out most of the data, so at least I can't read it.

MS. JENNINGS: On the one that discusses problem filters, there were 444 problem filters which amounted to 0.2 percent of all units filtered. Again, those are the ones that filtered, that took more than two hours or did not filter at all, so 0.2 percent.

DR. CHAMBERLAND: Of all units filtered were due to sickle. Thank you.

MS. JENNINGS: 0.2 percent were problem filters, and of that, 34 percent are sickle trait positive.

DR. RUTA: You mentioned that there were donors who I think were sickle trait negative, who failed to filter, who leukoreduced properly, is that correct?

MS. JENNINGS: Yes.

DR. RUTA: Those are 9 donors?

MS. JENNINGS: No, there were 47 donors who are sickle trait negative that were slow filters, that had WBCs greater than 5 x 10^6. What we found is there are 9 donors who repeatedly fail. They are all sickle trait negative. So, they would be into that 47.

DR. RUTA: So, no idea right now.

MS. JENNINGS: It is mixed, male and female, young and old. The only thing that may be common is most of them have elevated cholesterols. That is the only thing we can find.

DR. NELSON: Thank you.

The next speaker is Kenra Ford from the Oklahoma Blood Institute.

Kenra Ford

MS. FORD: Good afternoon. My name is Kenra Ford. I am Director of Laboratories and Inventory Management at the Oklahoma Blood Institute. I will be presenting to you our leukoreduction failure strategy.

[Slide.]

Obviously, strict process control, QC monitoring, and determining the potential failures, and as previously mentioned, sickle trait is one of several failures.

[Slide.]

To give you an overview of our filtration process, we filter red cells that have been precooled for a minimum of two hours. Our filtration is currently 100 percent sterile docked, and we do filter within 24 hours. Any units that do not filter within one hour are quarantined, and all quarantined red cells are investigated.

[Slide.]

To review with everyone what has happened to the white cell counting in the last couple of years, I want to give you OBI's history on where we were and where we are now.

A couple of years ago, we started with

Nageotte counting. When IMAGN was available, we implemented the IMAGN. We are probably on the IMAGN for about two years. Somewhere before last December, that all came to a halt and we came up on flow cytometry.

[Slide.]

The management of our sickle trait positive donors at OBI, and have been since I want to say September of last year, have been in the following. We have informed our donors that they have positive sickle trait results. We offer hemoglobin electrophoresis, and when they are notified they have a positive result, they are also currently redirected to a non-red cell donation.

[Slide.]

To date, this is our list of what we believe to be potential failures with leukoreduction, and obviously, sickle trait is up at the top, but not necessarily the most important nor by volume the most, the greatest, slow draws. Remember we are now in a 500 ml blood bag, and I believe that somewhere in all of this, going from a 450 ml blood bag to a 500 ml with the red cell volume somehow plays into some of our failures.

Our increased filter flow time and our

cutoff is set at an hour. Again, I mention increased packed red cell volume. This just came to the picture in about the last three months of data. On the higher end of the 500 ml collection, we are seeing more failure than on the lower side, and I just don't have enough information at this time to share except there seems to be something there.

[Slide.]

In addition, depending on which components that you prepare, may play a role into the residual white cell available in the red cell prior to filtration. That is whether you make a platelet, you don't, or whether you make a buffer or you don't.

[Slide.]

Our suggestions for in the future and currently what OBI's plan of attack is definitely further studies to determine what we just saw. Investigating the failures to completion and timeliness is critical.

Sampling errors are also an opportunity for what you think may be a failure, and we have come full circle with dealing with sampling errors, and while the filtering staff, we have had to deal

with ergonomic issues, we have also had the same with the increased number of samples that we are counting in order to hit the 1 percent plus to investigate all of the failures, and that is where time comes into play. It is very difficult on workload to deal with 70 to 80 white cell counts in a laboratory that was not previously used to dealing with that.

Continue with random QC and then also I believe that we have got specific donors that continue to fail donation after donation. We have put into place a mechanism to track donors that continue to fail the white cell counting based on their component tracking.

[Slide.]

Part of our plan of action for dealing with some of our failures, and clotting being probably the most significant reason for failure at OBI, is to implement the shakers during whole blood collection to minimize clotting events, and then also to manage sickle trait positive donors and then obviously the follow-up, as previously mentioned, with identifying based on our flow time.

Flow time of one hour seems to--and whether it needs to be 45 minutes or not, I don't

know--but seems to help us identify a significant number of failures that we would not have previously identified.

Currently, we are achieving less than 5 x 10^6 white cells per product 100 percent of the time, but our outliers are removed from our routine screening and QC statistics, and managed separately.

So, that is where we are.

DR. NELSON: Thank you.

Toby.

DR. SIMON: Two questions. What percentage of units are you losing because they don't filter, and you don't have a red cell product?

MS. FORD: They don't filter because of clot?

DR. SIMON: Whatever.

MS. FORD: Our data is a little skewed because we identify sickle trait positive donors and can remove those from filtration, prior to filtration, so we don't have to deal with sickle trait on a repeat donor.

So, if the rest is due to clotting, I would say currently, close to 1 percent.

DR. SIMON: Same as the Red Cross.

Do you screen all your donors?

MS. FORD: We screen all non-Caucasian donors as indicated on their donor registration form, and then screen 100 percent of our outliers based on flow time regardless of what is indicated on the DRF. The flow time of greater than an hour necessitates sickle trait as part of the investigation.

DR. SIMON: If they are identified as sickle trait, and you offer to redirect them, if they decline to be redirected to another program, and want to donate whole blood, do you still accept them?

MS. FORD: Dr. Gilcher?

DR. GILCHER: Toby, we don't have an answer to that one yet because currently they are being accepted for repeat whole blood donation, but, in fact, that is not a useful red cell in our system, so our plan is to work very hard, and we have, by the way, been successful in redirecting donors to non-red cell donations.

I think one other thing that I will mention, that I think is important here, is that we had to prove the success of the non-red cell

donations, that is, can these donors who are sickle trait positive, in fact, donate other products successfully, that is, a leukocytereduced platelet, so we have submitted a paper to the AABB in which we have used all of the three current technologies - Trema, Amicus, and Haemonetics LN 9000, and successfully collected platelets, and they are very easily leukocytereduced, in fact, they are below 10^5 many times.

So, there is no problem at all with the collection of platelets from these donors. So, that is our attempt, is to redirect them to platelets and to plasma, but definitely not to use them as red cell donors in the future.

MS. FORD: Of interest, when reviewing some statistics, we had a significant number of sickle trait positive donors that were already active apheresis donors.

DR. SCHMIDT: A question and a comment. Why do you ask them their race?

MS. FORD: Dr. Gilcher is going to answer.

DR. GILCHER: The reason I want to answer that, Paul, is that as part of the REDS Study, donors are, in fact, asked what their race or ethnic background is, and that is recorded and

captured in the computer, so we have that data.

DR. SCHMIDT: Now, the reason to ask people their race in the past was, and big movements nationally including the Red Cross, was to identify donors who might then be phenotyped, so you could provide red cells that were Cal and Duffy and E-negative to sickle cell patients, so they would not become immunized. So, you were looking for donors who would be good red cell donors for those patients.

Now, if you go into this, you can't use them as red cell donors, and I think somebody has to look at the bigger picture and find out if universal leukocyte reduction is worthwhile if it start causing things like this.

DR. GILCHER: Again, I am going to answer that question, Paul. It is a non-issue. First of all, remember that only 10 percent of, let's just take African-Americans, only 10 percent of them are, in fact, sickle trait positives. That still leaves 90 percent.

We have adopted red cell apheresis technology specifically the two red cell collection, and that has worked absolutely beautifully in our system to collect two units of

red cells from phenotyped donors.

We have literally many, many thousands of donors that we have phenotyped, captured that data in the computer, and we had one instance recently where we needed 25 units of red cells for actually a young woman with sickle C disease who was having a hip replacement and had to be exchanged, as well as have blood available for surgery.

We did that with 13 donors, 12 donated double red cell. She had 6 antibodies, by the way. Only 1 per about 8,000 units was compatible. So, we collected 25 units, of which 12 donors gave double red cells and 1 donor gave a single red cell. So, it shows how it can be done using the technology that exists. So, this is not a problem losing a very small subset that is 10 percent of the African-American donors. Still, 90 percent are available as phenotype donors.

DR. MITCHELL: I think it could be a problem if you tell people we want to know your race because we want to use your red cells for children who need your red cells because you are special, and then you end up really testing them for sickle, when that is not why. I mean that has to be done very carefully.

MS. FORD: Actually, our donors are informed that depending on what they request on their DRF, they are offer sickle cell screening and have been for 10 years plus at OBI. That is a very big incentive test for us, and that is not new. Taking this approach is not new for us.

DR. KOERPER: When we request phenotypically matched cells for sickle cell patients, we want those cells to be sickledex-negative. So, we are asking for sickledex-negative anyway. So, again, you are not losing a segment by doing the sickledex testing. We don't want to put any more sickle hemoglobin into those sickle cell patients.

DR. NELSON: The next is the open public hearing.

First, is from Pall Laboratories, Barry Wenz.

We have six people, so I just wanted to, if you could, be as brief as possible. Thank you.

Open Public Hearing

MR. WENZ: I am going to restrict the majority of my comments to our experience and the experience of some of our major customers with sickle trait donors and their impact on universal

leukocyte reduction blood supply.

As the major manufacturer and supplier of global filtration systems, Pall Corporation accepts its obligation and the benefits of enhancing products and processes by working with the regulatory agencies throughout the world.

In this regard, Pall was requested by the FDA at the conclusion of the January 2001 BSAC meeting to address the issue of blood obtained from sickle trait donors and the potential effect on the leukocyte reduced blood supply.

To accomplish this goal, Pall convened a Technical Advisory Committee, comprised of leaders in blood banking and transfusion medicine, as well as clinical practice, from diverse geographic areas of the United States. A series of questions were developed by some of the Pall participants, which in part were used to guide the discussion of the Advisory Committee. Specifically, these questions were:

What is the extent of the problem, that is, what is the percentage of the entire blood supply that is subject to the potential of containing sickle trait red cells?

Secondly, is the sickle gene solely

confined to one ethnic donor cohort?

Is it practical to screen all donors for sickle hemoglobin?

What is the correlate between sickle trait blood and white blood cell filter failures?

Finally, what is the impact of filter failures on the blood supply that is universally leukocyte reduced?

At the conclusion of the meeting, the following was summarized:

Firstly, data presented by the Technical Advisory Committee itself indicate that the incidence of sickle trait in the U.S. Afro-American population is 7 to 8 individuals per 100. The incidence of sickle trait in other populations is estimated at 1 in 10 to 1 in 40,000 individuals.

A random sampling of our customer base, as well as published literature and data supplied by several committee members, suggest that approximately 650,000 of the 13 million units of blood annually collected in the U.S. are drawn from populations with an appreciable risk factor for sickle trait. Of these, approximately 50,000 in total donors actually carry the sickle hemoglobin gene. This translates to one-half of 1 percent of

the U.S. blood supply.

These low incidence data support information previously reported to the Pall Corporation, which average an incidence of 3 failures per million filtrations which occur concomitantly in the presence of hemoglobin S. We realize that such instances are generally under-reported, however, even allowing for a 100-fold error reporting margin, this statistic is extremely low.

The question of whether there is a significant frequency of sickle donors for which filtration times are not significantly retarded, but rather, for whom leukocyte removal is reduced, was addressed by use of the Canadian model. Pall is the sole supplier of leukocyte reduction devices to Canada, and has been analyzing their data for approximately three years. These statistics were derived from urban areas where it is recognized there is an appreciable incidence of sickle trait.

The Leukotrap systems were evaluated at Pall Corporation while additional data were gathered during routine use from 16 blood centers in Canada that routinely use the system. A summary of the data is attached in the handout that was

available to both the members and the audience.

The numbers represent a sampling of 1 percent of the total number of units processed with the Leukotrap system. All of the red cell units, basically the sampling from 300,000 or a sampling of 3,103 units, processed with the Leukotrap system contained residual leukocytes below the regulatory guideline, the current regulatory guideline, of 5 x 10^6.

A majority of the red cell units prepared in these centers consistently attained low levels of leukocytes, typically 2 x 10^5 leukocytes per unit. Statistical analysis of the data at the 95 percent confidence interval shows that greater than 95 percent of the units labeled as leukocyte reduced products contained residual leukocyte contents within or below the required range.

In summary, the present results demonstrate that the Pall Leukotrap systems consistently produce red blood cell products that meet the most stringent regulatory guidelines.

In actual blood bank settings, 99.9 percent and 98.7 percent of the red cell units filtered contained residual leukocyte contents that were below 5 x 10^6 and 1 x 10^6 respectively.

In closing, I would state that the frequency of filter failures involving sickle trait donors, defined as slow filtration or failure to filter reported to Pall Corporation averages 3 per million.

Although this is an extremely low figure, and we allow for 100-fold margin of error reporting, the figure is consistent with the recently published information in the May 2001 regulatory update, in which the AABB states that the magnitude of the problem is relatively small, and further states that sickle trait testing, as proposed by the FDA draft guidance document, is not warranted based on this relatively small incidence.

Filtration which allows completion of the process, but produces unacceptable levels of leukocyte reduction, are also extremely small. The incidence is well below 0.5 percent based on the Canadian statistics analyzed.

Problems involving user error, failure to follow instructions, and failure to optimize internal procedures far outweigh the cause for failure to obtain leukocyte reduced blood.

ULR is a blood safety precaution and should be addressed similarly to serological

screening which accepts a low level incidence rate, of both false positives and false negatives. There are no precautionary measures currently employed to ensure the safety of the blood supply which has a specificity and sensitivity of 100 percent.

Finally, with the low level of sickle trait among African-American donors, the phenotypically distinct blood types needed for sensitized recipients are accessible from the greater than 90 percent of the population without sickle cell trait, as well as from a large number of non-Caucasian donors and Caucasian donors alike.

Pall will continue to work with its Sickle Trait Advisory Committee and looks forward to working with the regulatory committees in the future.

Thank you very much.

DR. NELSON: Thank you.

Questions?

Thank you very much.

Next is Steve Binion from Baxter.

MR. BINION: My name is Steve Binion from Baxter Health Care Corporation. Actually, I am going to restrict m comments to just a couple of points concerning CBER's response to this issue to

date, specifically, concern over leukoreduction of sickle cell trait blood.

Device manufacturers who had active product applications under review at CBER as of last December were contacted at that time and given two options. Number one was to perform additional performance studies with sickle cell trait blood or to add precaution statements in the product labeling related to potential failures associated with sickle cell trait blood.

We understand and support CBER's efforts in this area and are complying, but a couple of comments I think are in order.

Number one. These requirements, to the best of my knowledge, were communicated to manufacturers only in the context of product reviews that were active at that time. So, we would suggest or request that CBER identify a process to consistently apply these requirements across all filter products is this is a significant issue of policy for the agency.

Also, we would ask CBER to consider a letter to device manufacturers and the blood banking community to communicate CBER policy and requirements in this area.

Thanks.

DR. NELSON: Thank you very much.

The next is Celso Bianco, America's Blood Centers.

DR. BIANCO: I am sorry it is not going to be as short as the TRALI, but I will try.

We, ABC, obviously commends CBER for bringing up the issue of leukoreduction filter failures. We have submitted formal comments to FDA's draft leukoreduction guidance issued in January, and hope that FDA will address our concerns.

Today, I will address some of the most critical issues and will point out some additional concerns that we identified after we filed our comments. Our comments are a matter of public record. I will be glad to provide a copy to any interested party.

ABC members believe that CBER's regulatory approach to leukoreduction is inappropriate. Specifically, ABC members are being asked to implement quality control standards for the leukoreduction process including a new minimum level of residual leukocytes, extensive process validation, and a complex statistical process

control that did not exist at the time the devices currently available for leukoreduction were submitted for the 510(k) approval.

In our opinion, ABC members and other blood centers are being asked to perform activities that fall within the responsibilities of the filter manufacturers. For instance when the current generation of leukocyte filters were approved, the minimum standard for leukoreduction was less than 5 x 10^6.

In addition, CBER's previous guidance did not spell out requirements for validation and process control. Filter users have never been provided formal evidence, something like a summary basis of approval indicating that the approved devices meet the newly proposed standards.

Since ABC members have no control over the manufacturer of the filters, they believe that they are being unfairly asked to provide mountains of quality control data to document that filters approved under old standards meet the requirements specified by the newly proposed standards.

We define a filter failure as a unit of cellular product leukoreduced by filtration, that has a level of residual leukocytes that exceeds the

allowable limit established by FDA, currently 5 x 10^6 proposed 1 x 10^6.

BPAC should be aware that due to unavailability of automated cell counters, most leukocyte counts now performed are performed manually using Nageotte chambers. It takes between 15 and 20 minutes to visually count each chamber. This is a labor-intensive procedure difficult to perform under CGMP conditions.

Until recently we had access to an automated instrument for volumetric cytometry. The company that manufactured this instrument was sold to a manufacturer of flow cytometrists, and these manufacturers decided to withdraw the product from the market.

These reasonably priced and easily used instruments now are collecting dust or are being used as door stops in our blood centers.

The only semi-automated method currently available is flow cytometry, which is extremely expensive. Only one flow cytometry reagent is currently approved for counting.

Over the last month, we performed an extensive survey of our members, attempting to correlate filter failures with conditions of use.

We obtained responses from about half of ABC's 75 member centers. Those, in aggregate, distribute 1.2 million units of red cells a year, 51 percent of which were leukoreduced, and the survey covered the period of November 2000 to April 2001.

Eight of those centers are leukoreducing more than 90 percent of their red cells, 16 leukoreduced between 20 to 90 percent, and 12 centers are at less than 20 percent.

We found substantial variability in the results. For instance, when the cutoff was 5 x 10^5, all but one center had failure rates of less than 1 percent, consistent with what has been presented today. The outlier had a rate of 2 percent.

Depending on the geographic location of the center, a small fraction of these failures were associated with sickle cell trait as defined by a solubility test, not a hemoglobin test. Eighteen centers provided data about failures when the cutoff was less than 10^6.

Three had a failure rate of 1 percent or less. Seven had failure rates of between 1 and 3 percent, and 8 had failure rates that exceeded 5 percent. Among the latter, 3 large, highly

sophisticated blood centers, including one that provides 100 percent leukoreduced red blood cells had failure rates over 12 percent at the 10^6 cutoff.

There was inverse correlation between the use of shakers and filter failures using the current 5 x 10^6 standard. The average failure of centers that did not use shakers was 0.9 percent, close to 1 percent, while those using shakers, 50 percent or more had failures close 0.2 percent, that is, 5 times less.

There was no clear correlation of filter failures with temperature of filtration cold room or room temperature, center size, nor with the percentage of African-American donors.

Furthermore, some of the 8 centers that perform 100 percent leukoreduction that are presumably skilled in applying the technology had high filter failures when the 10^5 cutoff was used.

It is important to note that ABC centers most likely experience far more filter failures than they reported in the survey due to the lack of appropriate instrumentation for leukocyte counting.

For instance, the overall failure rate at 5 x 10^6 was 0.7 percent, but the two centers that

were still able to use the IMAGN during the survey time had a failure rate of 2.2 percent, and we wonder if this wasn't because they could count better more and more often.

A number of papers presented at meetings and in published studies, most of them performed by ABC member centers, showed that many of the red blood cells collected from donors with sickle cell trait failed to meet the old and newly proposed standards upon filtration with currently approved device.

However, the literature in our ABC member survey indicate that sickle cell trait is a minor contributor to leukoreduction failures. Unfortunately, the majority of failures are related to the fact that manufacturers have not yet established process conditions that produce consistent results at the lower cutoff for residual leukocytes.

Our centers are diligently attempting to define the right conditions. For instance, some have adopted, as you heard today, a time-based approach, units that take longer than an hour to filter are subject to quality control. However, our centers do not have the resources, time, and

personnel required to perform the operational research required to bring this 510(k) approved filters and processed into compliance with the proposed guidelines.

We believe that this should be done by the filter manufacturers.

I would like to make some suggestions. We think that BPAC should consider the issues presented today and in comments to the draft guidance before making final recommendations to FDA regarding levels of leukoreduction, validation, quality control, and other procedures that address leukoreduction failures.

Similarly, BPAC should defer recommendations regarding the management and deferral of donors with sickle cell trait until more data becomes available and there is extensive discussion about the implications of screening of blood donors for sickle cell trait.

This discussion must include sickle cell researchers, treaters, patients, and their families. FDA should delay publication and enforcement of the draft guidance until the device approval of all filters marketed in the U.S. is reviewed for compliance with the new draft

guidelines and filter performance is documented by the manufacturers and automated counting equipment is available.

Before enforcement of the guidance, FDA should require new labeling--and I just realized or heard that FDA has approached manufacturers for that, and I am pleased--for approved filters. Our dream is that the label of the filter package will say that this filter will produce more than 95 percent of the cellular components will contain less than X x 10^6 residual leukocytes per ml.

Detailed manufacturer's instructions and recommendations including process requirements, such as time after collection, temperature of filtration, expected time of filtration, maximal allowable time for filtration, and recommended procedures for investigation of filter failures.

Also, a customer complaint system reporting mechanism for manufacturers that includes analysis and corrective actions that they must follow. This process must include timely communication of process changes and events that affect filter performance to its customers.

In essence, ABC member centers are asking that filter manufacturers and FDA provide us with

the appropriate devices and tools before they ask us to apply burdensome standards akin to those applied to blood donor screening tests, and I am glad that Dr. Wenz mentioned blood screening tests.

Can you imagine what would happen if screening tests for infectious disease had such unclear manufacturer's instructions, variability, and rates of failure?

We sincerely hope that the information discussed today will guarantee a more rational and balanced approach to the new guidance and to the future of implementation of leukoreduction as recommended previously by this committee and recently by the HHS Committee on Blood Safety and Availability.

Thank you.

DR. NELSON: Thank you.

Next is Loren Acker from SEBRA.

MR. ACKER: My name is Loren Acker. We are the developer of the SEBRA shaker, which is part of the Canadian success, and I am here principally as an engineer. I can't help you at all with analysis or discussion about sickle cells, but I can tell you statistically, in our opinion, that most clotting or clogging of filters is not

driven by sickle cells. I think you have already heard some of the statistics that will support that.

Just a little history. We developed the original shaker in 1978 for Dr. Van Schooenhaven at Blood Systems and Dr. Carlos Ericks at the New York Blood Center. It was widely but not universally adopted except in Canada. Canada put it into place in approximately 1980, and it continues to use it exclusively through today.

It has gone through a major renovation or upgrade in 1990, which is being implemented in the last few years. It adds more vigorous mixing, further reducing this problem, as well as flow control, which prevents another cause of clotting and filter clogging, and that problem has to do with bleed time.

Bleed time is very, very important. So, if you have bleeding rates that are longer than 12 minutes, you probably are going to, even with good mixing, you are probably going to have some clotting problems.

In any event, you have to think about this beyond just the discussion on sickle cells. The other issues are mixing, bleed time, and in certain

procedures, stripping, where there may be clots accumulating in tubing that is then subsequently stripped into the blood unit.

We have done an informal survey with approximately 12 customers, it is fairly random, but definitely not scientific, but I think the results are something you need to duly focus on.

Those centers that mix 100 percent of the time have a filter failure rate from all reasons that are less 0.3 percent. That is less than one-half of 1 percent. Based upon our survey, all centers that are doing manual mixing have a failure rate that exceeds 1 percent.

Now, you have heard some numbers that are a little bit different than that, but our experience is all but one that we have contacted have a failure rate of greater than 1 percent, and in some instances, up to 4 percent.

There was one sharp exception to that, which was at six-tenths of a percent. We personally went and visited that center to try to figure out how they were getting such low results with manual mixing, and what we found was an extremely disciplined management and phlebotomy staff that literally removed the bag at least once

a minute from the scale--this is a manual scale now--and mixed the bag by tilting it end to end three times, at least five or six times every donation. That is a very labor-intensive process, but the managed to get their statistics down to 0.6 percent.

In any event, in summary, keep in mind that sickle cells account for less than half of filtered clotting. We can do a great deal about the other part, and that mostly has to do with mixing, and that is my conclusion.

Thank you.

DR. NELSON: Next is Dr. Jeanne Smith from the NHLBI Sickle Cell Advisory Committee.

DR. SMITH: Good afternoon. I would like to thank the advisory committee for the opportunity to speak and to thank the previous speakers for having covered many of the issues that I covered briefly in my remarks, which have been distributed to the committee members, so that I don't have to touch on them now.

Let me say, though, that I have learned a great deal more in the course of the day listening to the various and sundry comments that have been made concerning the problems, first of all, with

filtering blood, and the things that we don't know yet concerning the types of filters and the variance in their success, the temperature at which blood is filtered, shakers, the length of time to bleed the donor, user errors, and I could go on, but I won't. I think the message is there.

There is a lot that needs to be done. The problem is not just a problem of sickle cell traits. This is a problem, but this is not the only problem.

We live in a country where there is always a shortage of blood, and we really cannot afford to lose any more units than we have. I think Dr. Bianco's comments about putting the burden on the blood bank in terms of very rigorous QC which is not backed up by the ability of the manufacturers to provide the equipment, that you need to do this. I don't run a blood bank, I just run a simple hematology lab, but I can understand his pain a great deal.

I think, though, the thing that I would like to spend my time, it has been touched on, but I want to put this in a little perspective, is the issues concerning sickle cell trait.

I think many of you are aware that since

approximately 1972, there has been, on a national level, a sickle cell program. In addition to the sickle cell program, we now have a nationwide genetic disease program, which in some ways has used the sickle cell program as a prototype, since this was one of the first genetic diseases that was really addressed in the country.

This involves a great deal, and it is not just the management of the disorder, it involves the screening, the need for informed consent prior to screening, the need for post-screening counseling, the need to do these things in a way which does not allow for any implication of discrimination, and I think, most importantly, the need to run any program in such a way that an erroneous message is not delivered to those individuals who are being tested.

What do I mean by this? Very simply, I mean that at no point should we be delivering a message that the individual with trait has any clinical problem which would put them at risk or would put the recipient of blood from them at risk. We just can't do this unless we know what we are saying.

I think it is important that we remember

that while transfusion of red cells is the present topic, donor status also refers to donation of organs, also refers to donation of bone marrow, both of which are areas in which donations from donors who are HLA-identical and probably family members are most ideal.

Anything that this committee does needs to look at what kinds of an effect. I would ask the committee to look carefully at what has been done in the past, what federal policy has been done in the past, and not to attempt to establish a new policy without serious consideration of those policies which already exist.

Thank you.

DR. NELSON: Thank you.

Are there questions or comments?

Thank you, Dr. Smith.

Jim O'Connor from HemaSure.

MR. O'CONNOR: On behalf of Whatman/HemaSure--we are now Whatman/HemaSure--I would like to thank the BPAC Committee for allowing us to address you.

Leukoreduction failures are attributed to component processing procedures, characteristics of the blood units, and the filtration device, as we

have all heard today.

As a manufacturer, we have really the obligation and the responsibility to investigate all the responses and to the feedback that we get on the use of our products.

[Slide.]

What I would like to do is to sort of describe that process that we go through and then go through two examples that you have heard a lot of today, about what these leukoreduction failures are.

Whatman/HemaSure response to experiences with our products is guided by a mission and a strategy that we launch at the time of the product conception. Active monitoring of the product is part of the service that we provide with the product. Information and data is continuously compiled and compared to the product specifications, and requirements are established or reinforced as a means to direct investments in studies, improvements, and in new products.

Such studies can include epidemiology, pathophysiology, and various engineering and technology developments. These activities extend the envelope with the knowledge and medical device

evaluation and testing. Investments in these areas are part of a manufacturer's commitment to the business and the customer and the patients.

The feedback loop depicted in this schematic is business practice. The operating elements of this business practice are contained in our quality system.

[Slide.]

The key elements of the quality system are listed here. The quality system is derived from the ISO-9000 and the FDA QSR guidelines. This system tracks documents, a product, from conception through the product life cycle.

The basis of a filter's performance, its claims are in this documentation system. The conditions for use in testing are documented here, and it is called a Design History File. This documentation is a technical reference for addressing customer complaints or, as we sometimes refer to them, as customer experiences.

[Slide.]

Our experience in leukoreduction filtration comes from design and testing of filters at our facilities and direct feedback from our users through our Technical Service and Customer

Service groups.

Laboratories at Whatman/HemaSure procure and process two- to three-day-old red blood cells routinely to monitor product performance. Field personnel work directly with blood centers during a two-day training and implementation program that includes an assurance of a successful validation. Routine follow-up visits and visits following complaints are conducted to monitor the filter's performance.

Various types of filtration processes are witnessed, and the feedback is fed through a transfusion safety program.

At this point, I would like to focus on a couple of our experiences with stop filtrations in high white blood cell residuals. These, of course, are going to be associated with red cell filtrations.

[Slide.]

This is a very simple chart. I hope it is graphic enough to represent what we perceive as the leukoreduction failures due to the high white blood cell residuals. These are a small fraction of the experiences that are reported to us.

[Slide.]

Less than a hundredth of a percent of our observations are associated with high white blood cell residuals. Review of the processes and filters associated with these observations do not always give a reason for the high white blood cell residuals. Issues that we have been able to attribute to these white cell residuals are, as mentioned earlier, clot formation and sickle cell trait positive donors.

Sample preparation and counting methods also come into the picture. Awareness of the training usually improves the component process related issues, however, there are still a lot to go in the investigation. We test all filter lots at our company for white blood cell residuals, and we review these records to ensure that the testing does not correlate to the high white blood cell residuals that any customers observe.

[Slide.]

The next experience I think has been dwelled on a lot today, and it is our experience, as well. It is the largest issue that we see, and it is the stoppage of flow and sometimes called clogging.

[Slide.]

As seen in the previous slide, this constitutes the largest experience. As you would expect, this can lead to 85 percent recovery issues, but that is a small portion of what we see.

We have not been able to relate this issue to high white blood cell residuals in our labs as others have reported earlier, however, we have documented and proved white blood cell residuals coinciding with training and awareness on proper mixing during blood collection, proper mixing during blood component preparation, and proper mixing prior to RBC filtration.

This work was presented in an ISBT poster in Vienna last year.

[Slide.]

I would like to also note that some of the osmolality shift suggested earlier--and today I have learned quite a bit about what the sickle cell trait is--the additive solutions going into the cells, as well as the anticoagulants do create osmolality shifts, and hypertonic situations can change red cell morphology and even red cell rheology, which would affect filtration processes.

[Slide.]

To conclude, most important lessons that

we have learned from our experience with leukoreduction filtration is that the quality of the outcome is dependent on the component process preparation, on the training, and also on the filter.

We have also learned that you have to remain committed to the quality improvements and the support of the blood centers to improve the transfusion process.

Thank you for your attention.

DR. NELSON: Thank you.

Questions, comments?

[No response.]

Committee Discussion

MS. POINDEXTER: We have four questions for the committee.

Do the committee members endorse donor screening for sickle cell trait as a strategy to prevent leukocyte reduction filter failures?

DR. NELSON: Comments from the committee? Yes.

DR. SIMON: I certainly impressed by Dr. Smith's written comments and her statements, and by the data presented that shows the relatively low percentage, and I would certainly urge that we not

do that, and answer that question no. I think that there are just a lot of problems with proceeding with that approach, and it doesn't appear to be a clear answer. It kind of leaves the blood centers ad hoc to figure out what to do with these failures, but I think that is the path we need to take.

DR. STRONCEK: I agree that it is not a good path to take to screen blood donors for sickle cell trait. Really, this is a problem that just everybody has become aware of since last fall. So, I think there are things to investigate and things to try to get around this issue without having to test these donors, and it would be worthwhile to give investigators time to try and work through these problems another way.

DR. NELSON: I wonder, is there any experience that talked the method of collection, temperature, the shaking, et cetera, would obviate any problems with sickle cell trait?

DR. SIMON: The only thing I could hear from the presentations, perhaps going to colder temperature might help or the higher volumes with the lower concentration of anticoagulant is seen possibly to contribute. I don't know, David, you

know more about it.

DR. STRONCEK: Could that be done routinely without screening, is that what you are saying?

DR. SIMON: I guess one of the things that could be looked at is whether refinement of technique reduces that part of the problem. The other problem doesn't relate to sickle cell. So, that is some of the data that needs to emerge as time goes on.

DR. STRONCEK: We are collaborating with Connie Noguchi to look at some of the issues she mentioned as maybe having factors involved with polymerization of hemoglobin S in the blood bags, and the results are too really preliminary to comment, but there is plenty of things to try, and we think we can get around the issue.

DR. NELSON: I would endorse what Dr. Stroncek has just said. I have been a bit underwhelmed by the lack of involvement of people with sickle cell expertise other than Connie and what was described earlier today. I think that there is a good change that there will be a technical fix that will come out of good studies based on some of what is known about sickle

hemoglobin.

DR. CHAMBERLAND: I would concur with all of the comments that have been made. I think it is premature to make a recommendation. The data that have been collected, as has been mentioned, have been done under actually in the time allotted for the presentations, it is hard to even get a complete picture of the variables that might be important and impact whatever they would be, temperature, shaking, technique used, type of filter, definition of failure, et cetera. So, it is really impossible from this brief review of the data to even try and pull together any common thread.

A couple of things impressed me. One was in the large databases, particularly the Red Cross, seeing what a low proportion of the failures were due to sickle trait when that was evaluated, but I think what really took me aback and is a cause of concern is that the overall rate of filter failures and subsequent loss of red cell units approaching 1 percent is really of grave concern particularly as we stand on the threshold of potentially further shortages that may be incurred as a result of expanded CJD deferral criteria.

So, there is, I think, a fair amount of urgency to put together the combined efforts of industry, government, and private academia to try and look at this in a fairly short time frame for reasons that I had not originally anticipated.

DR. NELSON: I was a little confused, too, and maybe the FDA could clarify, there was talk about two standards, one 5 x 10^6, their low, and one is 1 x 10^6, and it looked like the more rigorous one was met with much greater failures.

What is the FDA's position now and in the future?

MS. POINDEXTER: Well, the current standard or the current memo that was out in 1995-1996, the goal was to meet 5 x 10^6. The current guidance document that is out in draft from is suggesting that the blood centers attempt to meet 1 x 10^6 with the 95 percent confidence interval.

It was our feeling at the time that from the data that we had received from the manufacturers, that those filters should perform to that level and actually could exceed that level quite nicely.

What we didn't anticipate were the reports

of the AABB where, anecdotal as they are, a number of centers were pursuing the sickle cell trait problem as one that they could identify and test for, whether they test the donor or whether they test the unit as it is failing to come through the filter, it was something that there was already a test available, and we fully realized that there are social problems with that, whether we test just African-American or whether we test everybody.

DR. SIMON: I was just going to comment on the standard. I can understand this approach, and I guess I am not suggesting that we prevent people, like to people from Oklahoma or Texas, from pursuing it, but I just don't think that we should make it a national standard.

I agree with the urgency. I know that this is not the time or place to reconsider the issue of universal leukoreduction, but with those numbers, I think that Mary pointed to, which I had asked Dr. Haley about, it does bring up the issue of your cost-benefit - are we going to cause more harm with universal leukoreduction than we do help.

If possibly in a short period of time, the manufacturers and the blood centers together can get that weighed out, perhaps by the shaking and

more attention to some of the detail, then, perhaps that urgency is not as great as we thought. But that is where I think the focus needs to be.

DR. LINDEN: I just want to say this is an issue that I am very concerned about, and I am glad it is getting more attention because I think it has been somewhat neglected. I am also concerned about the lack of data. I think we need more data, not only about why this is happening, but the frequency.

I am a little concerned about some misleading data. If you don't test all of your filter failure units for sickle, you don't know what the cause is, and in some cases, you know, people haven't done that. So, I think that would be an important step, to identify the frequency, but certainly based on some of the data that we did see in that regard, this is only one component of a much larger problem of filter failure.

I think that there is other things certainly that need to be looked at including, you know, the use of shakers and some of the other things that people have talked about, so that it would certainly be premature at this time, but it is an issue that really needs to be looked at

closely.

DR. NELSON: Could we vote on this then?

All of those voting yes?

[No response.]

DR. NELSON: All of those voting no?

[Show of hands.]

DR. NELSON: All of those abstaining?

[No response.]

DR. NELSON: Consumer?

MS. KNOWLES: No.

DR. NELSON: Industry?

DR. SIMON: No.

DR. SMALLWOOD: The results of voting on Question No. 1. There were no YES votes, 12 NO votes, no abstentions. Both the Consumer and Industry representatives agreed with the NO vote.

MS. POINDEXTER: Question No. 2, please.

Please comment on experiments that might be performed to determine conditions that would allow filtration leukoreduction of blood from donors with hemoglobinopathies such as sickle cell trait.

DR. NELSON: We have already discussed that to some extent. It is not a yes/no, but you have our comments.

DR. NELSON: The third question.

MS. POINDEXTER: Please comment on any additional strategies that could be pursued to reduce the incidence of leukocyte reduction filter failures from clots and other causes.

DR. NELSON: Comments on that?

DR. SIMON: I think we have discussed that.

DR. NELSON: And then the fourth?

MS. POINDEXTER: Question 4. Should the labels on leukocyte filters be revised to address performance limitations including (a) expected filtration time; and (b) the risk of failure in donors with sickle cell trait?

I would like to amend Item (a). There is a section in the Device regs that insist that the labeling include the application time for the filter or for the device that is in use. So, that one really doesn't have to be discussed. That will have to go on the labels, the proposed application time based on the manufacturer's experience.

DR. NELSON: I am not sure that the data are all that solid to put a label on with regard to what the expected failure for sickle cell at present. I mean we certainly need more data on

that, but not enough to put on the label, I wouldn't think.

DR. SIMON: I would agree. I was just going to ask, Betsy, there is a distinction being made here between the label and I guess the more extensive package insert?

MS. POINDEXTER: The labels that I am aware of for the filters are really rather abbreviated, and they would be, yes, the instructions for use or directions for use. It is not the label that comes on the filter so much as it is the instructions for use.

DR. STRONCEK: I guess I disagree. I feel strongly they should put that on the label because I think Pall basically got up and denied that is a problem. At least in my mind it is. I mean to me they are behaving like cigarette smoking doesn't cause cancer.

I think that if we make them put this on the label, then, when they come along with a new filter, they are going to be damn sure they check these filters out in patients with sickle cell trait.

Otherwise, they are just going to go on and deny this is a problem. They are going to come

out with another filter. They are not going to test it in patients with sickle cell trait. Then, we will be sitting here again with the same problem.

DR. SIMON: We are talking about the manufacturer's instructions here.

MS. POINDEXTER: Yes, again, the instructions for use. As. Dr. Binion stated, we have been asking manufacturers who have currently pending NDAs for 510(k)'s for red call or whole blood leukoreduction filters to include that labeling unless they have run studies to show that they do successfully filter.

DR. SIMON: So, you are asking us basically to support your policy.

MS. POINDEXTER: Yes.

DR. NELSON: Do you want to vote on this one? Any other comments? John.

DR. BOYLE: Just a question, and that is if we vote yes on this, we are requiring it of all manufacturers, but if we vote no, then, new manufacturers who are applying can be required to do it, but it will not apply to all manufacturers, is that correct?

MS. POINDEXTER: I think that what we

should is probably take Dr. Binion's approach, and that would be have FDA/CBER send a letter to all filter manufacturers requiring this to be on all of their current labeling unless they have performed such studies, at which time they would have to present us with a new NDA or 510(k) submission.

DR. HOLLINGER: Along these same lines, it seems to me as I looked at this draft guidance, the one that is not for implementation, they ask for comments, and so on, but the issue is it seems like it places a lot of burden on the blood bank when many times it ought to be placed on the manufacturer in terms of their performance, and so on.

It seems like it is very rigid if you have even an unacceptable unit. If I read this correctly, just one unit that is unacceptable, you know, in a three months period of time, if I am reading this correctly, then, they have to go through a whole lot of testing of 60 units and other things, too, and the question is who is paying for those 60 units to do all the testing, and so on.

That also seemed very rigid to me in here, and I think from my standpoint it ought to be

higher than that if they have more unacceptable units, because what I heard today was the manufacturer speaking to the fact that they don't see that much of a problem, and yet the blood banking community say there seems to be a problem here with a large loss of units.

Now, it may be because, number one, they may not be following manufacturer's guidelines or instructions, and if that is correct, then, it ought to be so noted, and the instructions ought to be very clear about how then one can get down to three-tenths percent or four-tenths percent, of something of that nature. That was just a comment about the guidance.

DR. CHAMBERLAND: I guess the way the question would now read is that we are only going to vote on it with clause (b), since (a) is a requirement. I guess I am still somewhat bothered about just having that as the sole--it won't be the sole thing, this expected filtration time is still going to be in the package insert, but it seems to me that based on what we heard today, there might be a variety of conditions or situations with shaker, without shaker, 4 degrees, room temperature, or whatever, that you would want to

have performance data on, and maybe that is a routine part of these package inserts, I don't know, but I am just sort of struggling with something that just doesn't seem quite right, particularly when the whole sickle cell trait story hasn't really evolved yet.

DR. NELSON: I think on voting on the first question, we said more data is needed, and there are issues about shaking and temperature, and all this, and this just isolates one of the issues.

It seems to be kind of incomplete and it doesn't certainly tell the whole story, and may not tell the right story.

MS. POINDEXTER: Could you suggest a way of modifying the question, should we modify it, for example, that units that filter in greater than so much time must have quality control. I mean we don't want to do that, that QC burden on blood banks would be incredible.

DR. CHAMBERLAND: I guess I just personally don't feel at this moment in time, with the information that has been presented, that certainly I could come up with some comprehensive list of conditions that should be included on a package insert.

DR. NELSON: This device may fail for a variety of reasons. Smoking is dangerous to your health.

[Laughter.]

DR. CHAMBERLAND: I mean I think there needs to be a thorough review of the existing data, more thorough than what we might be able to do in this kind of a setting. It seems to me that there has been a fair amount that has been collected, and we have seen a snapshot of it, but more detailed with people with good technical expertise and access to be able to sort of review it in a more systematic and comprehensive fashion might help.

MS. POINDEXTER: But what we have also heard is that from the Red Cross experience, they have had 30,000 filter failures, of which virtually none of them have been investigated because of the time involved in the way that the recordkeeping is kept, so that, you know, this wealth of information that you can't get to.

DR. CHAMBERLAND: Unknown is the biggest culprit.

DR. STRONCEK: I think based on what we have heard today, a blood manufacturer would be crazy not to collect blood without one of these

blood mixers. I don't know if it came out, but some centers don't have these rockers, the shakers, and the second issue is I think it is clear that sickle cell trait blood is a problem with filtering. What is kind of murky is what about all the other problems and how to fix that.

I think you have to start to fix what you know and what you can fix.

DR. LAUCHENBRUCH: My name is Peter Lauchenbruch. I am Director of the Division of Biostatistics at CBER.

Just going back to the comment that you made on the rigidity of the requirements, the testing is looking at 60 units, and if one sees zero failures out of 60, the upper limit of the confidence interval for that is 5 percent. So, if you see more than 1, you have a failure rate that clearly does not rule out the 5 percent, so that is why the requirement for looking at a larger sample of continued sample was suggested.

DR. McCURDY: It seems to me that we have, as has been discussed, precious little data on what causes this other than clots and perhaps sickle cell trait. Actually, what I heard today, and I have heard in the past, we really can't be sure how

many of the clogged filters are sickle cell trait and how many of them might represent a sickle cell hemoglobin C disease or a sickle cell beta plus thalassemia or something like that, because sickledex is not, a solubility test is not an acceptable way of making a diagnosis of sickle cell trait, at least by itself.

I think that the biggest recommendation that I would make is to take filter failures and evaluate them for things that might increase the rigidity or decrease the pliability of red cells. For example, hereditary spherocytosis, there are many patients with that who are more yellow than sick, have normal hemoglobins, and the spherocytes almost certainly won't filter.

If they have had an splenectomy, then, they won't even have hemolysis anymore, and they won't filter, and Lord knows what other things that might affect the plasticity of red cells might be involved.

What we have got is passive surveillance with very limited evaluation following the discovery of a failure with perhaps a few exceptions, but it is really very poorly studied thus far.

DR. RUTA: I think what the committee is saying is what we are saying, is that as the country starts implementing leukoreduction, we start to see failures, some of which were unanticipated, and some of which might have been anticipated, and I think as we learn more and as causes are investigated to find other conditions, we can consider additional labeling as it becomes more definitive as to what will cause failures, if that helps the committee.

DR. NELSON: Should we vote on this?

Voting yes?

[Show of hands.]

DR. NELSON: Voting no?

[Show of hands.]

DR. NELSON: Abstentions?

[Show of hands.]

DR. NELSON: Toby?

DR. SIMON: I guess I will go with the yes.

DR. NELSON: Results of voting on Question No. 4, and I will read it as it has been modified.

Should the labels on leukocyte filters be revised to address performance limitations including risk of failure in donors with sickle

trait?

There were 2 YES votes, 4 NO votes, 5 abstentions, and the Industry representative agreed with the YES votes.

DR. NELSON: The next item is Report of the Intramural Site Visit of the Laboratory of Plasma Derivatives, Division of Hematology.

VI. Report of the Intramural Site Visit of the Laboratory of Plasma Derivatives, Division of Hematology, OBRR

Neil Goldman, Ph.D.

DR. GOLDMAN: Good afternoon. I am Neil Goldman, the Associate Director for Research at CBER. I would like to thank you for allowing me to present today a brief introduction and overview of the CBER research that goes on and the process for peer review.

[Slide.]

As you undoubtedly know, the mission of CBER is to protect and enhance the public health through regulation of biological products including blood, vaccines, therapeutics, and related drugs and devices including those that you have heard about today, leukoreduction devices.

The regulation of these products is

founded on science and law to ensure their purity, potency, safety, efficacy and availability.

[Slide.]

Hence, we conduct research as an essential element of science-based decisionmaking on regulatory issues, and see research as the linchpin to our other areas of regulatory responsibility, which include review of product submissions, development of regulatory policy, product surveillance, which entails lot release testing, inspections, adverse event monitoring, as well as manufacturing compliance and the enforcement aspects that go along with it.

[Slide.]

As you are also already aware, product review and approval are among our primary responsibilities, and we have scientists and medical officers who do full-time product and clinical review, but in addition, we have lab-based senior investigators and what we call conversion track fellow, also referred to as tenure-tracked fellows, spending about half of their time on products and clinical review, and half of their time on regulatory research, as well.

We refer to these staff as our research

reviewers.

[Slide.]

The research reviewer model ensures that CBER researchers are fully integrated into the regulatory process. Their regulatory duties include review of INDs and BLAs, development and presentation of regulatory policy, meetings with manufacturers, as well as with the Advisory Committee as we are doing today, and they also may be performed by prelicense inspections.

This in toto, then, is what we refer to as the researcher/reviewer model, which an external committee for the review of CBER research, which was a blue-ribbon panel that evaluated CBER's entire research program back in 1998.

They commented in their report that the researcher/reviewer model is essential to providing CBER with top level expertise in a regulatory culture.

I would like to remind you, by the way, that although I have mentioned that they spend roughly half their time doing regulatory work, implying that they spend half their time doing research, probably at this point that is less than accurate. They probably spend certainly more than

half their time doing regulatory work.

[Slide.]

Now, CBER actually has quite a proud tradition particularly in the area of product-related research. In 1955, about 17 years before we became a component of FDA, and while we were still part of NIH, we were mandated by the PHS Order that we shall conduct research on problems related to development, manufacturing, testing and use of vaccines, serums, antitoxins, and analogous products including blood and its derivatives. We shall conduct other studies to assure safety, purity, and potency of biologic products, to improve existing products, and to develop new products.

For the last approximately 45 years, we have considered this our charge. Of course, we have broadened the areas to include other products, the new products, such as the cytokines, monoclonal antibodies, cellular and gene therapies, and soon, who knows, it may be human cloning, as well as tissues for grafting and xenotransplanted organs.

[Slide.]

Currently, at CBER, we have approximately 420 lab-based scientists, of which there are about

76 who are referred to as permanent career appointment principal investigators, and another 58 who are what we refer to as the conversion track investigators. Again, this would be similar to the tenure-track investigator out in academia.

We also have approximately 96 contract postdoctoral fellows and about 193 technical support and staff scientists.

[Slide.]

Now, the types of research performed in this center include: first, research on a specific product including such aspects as mechanism of action, potential toxicity or surrogate measures of efficacy; second, research on a specific policy issue, which may be related to a product class, as you heard today, disease area, or therapeutic modality; and, lastly, and of major importance to a regulatory agency like ours, research associated with the development and validation of methods and standards to maintain product safety and quality.

[Slide.]

More specifically, the mission-relevant program areas which cover most of the research actually being done at the center include such things as physical/chemical characterization of

products, determination of adventitious agents present in products, standards and methods development, determination of mechanisms of immunity, disease, pathogenesis, or toxicity, biological responses and mechanisms of action of biologicals, and lastly, clinical trial design and analysis.

[Slide.]

The vigilant oversight and quality control of our research programs are maintained through our continuous intramural review of our research. We site visit, review our laboratory research programs and the individuals who guide them every four years by an external Peer Review Committee composed of members of our Advisory Committee, a committee like this, in concert with outside experts, and these would be experts from academia and other research institutions, who are in the particular field of study of the laboratory to be reviewed.

Now, for our approximately 30 laboratories in the center, this turns out to be about 6 to 7 lab reviews per year. In addition, internally, our office directors for each of the product offices that have research, using criteria for mission relevance and scientific excellence, have been

prioritizing their research projects and funding them accordingly.

Lastly, as I previously mentioned, we underwent an external review of the center's entire research program, and this was indeed a review of the 12 research divisions that were currently in the center back in 1998. That has since been changed to 10 research divisions.

[Slide.]

Now, the site visit team, a subgroup of the Advisory Committee, and in this case the subgroup was of BPAC, was charged to assess--and that is both assessing the strengths, as well as the weaknesses--the quality and appropriateness to the regulatory mission of the research that was being conducted, which included the relevant scientific rationale, validity of approaches, creativity of design, and solution and levels of sophistication.

[Slide.]

And also to evaluate the accomplishments of the individual scientist, that includes demonstration of his or her abilities in experimental design and performance, independence of effort, originality, stature and recognition

amongst his or her peers, and productivity.

[Slide.]

In addition, we asked the site visit team to provide us advice on the current scientific direction of the research program, whether new directions should be considered, any changes in the way the research program is administered or the level, and utilization of resources in that program.

And lastly, any advice on promotion or conversion of eligible candidate, particularly the appropriateness at this time for such a personnel action.

[Slide.]

A final draft report is then prepared by the chair of the site visit team, and we were honored to have Dr. Nelson as the site visit chair, and he was helped with preparing this report from his ad-hoc reviewers.

This report then is presented to the full Advisory Committee, in this case the entirety of BPAC.

Now, as the parent Advisory Committee, you, BPAC, have the honor and duty to accept, reject, or modify the site visit report in part or

in its entirety.

Then, lastly, you will provide a final approved report, which is then sent back to our center director, who then passes it back down the chain of command to the particular investigator who was indeed reviewed.

If a recommendation is required, one will be prepared and sent back here to BPAC.

[Slide.]

Now, our internal Promotion and Conversion Evaluation Committee will use the final approved site visit report from BPAC as significant evidence to support either a candidate's conversion to permanent employment status or his or her promotion to the next grade level.

[Slide.]

So, in conclusion, I would certainly like to thank you very much, particularly Dr. Nelson, for the great job he did in shepherding the site visit review, and I would also like to thank the persons that actually were on his review. Now, I don't see Dr. Kagan, but, in fact, Dr. Kagan was one of the members, and we certainly appreciate that.

I would also like to express our deep

appreciation to BPAC for supporting our need to peer review our research programs, particularly in these times of fiscal austerity. The programs that you will hear about, and certainly briefly, prior to going to closed session, entail three principal investigators in the Laboratory of Plasma Derivatives, and one investigator in the Laboratory of Cellular Hematology, and they are in the Division of Hematology.

In fact, the next speaker, Dr. Finlayson, will give you a more focused view of the needs of the Office of Blood and that particular division.

So, I thank you, and if there are any questions, I am willing to take any right now.

[Pause.]

DR. GOLDMAN: It doesn't seem like it. So, Dr. Nelson, it is yours.

DR. NELSON: John. Dr. Finlayson will tell us about the organization.

John Finlayson, Ph.D.

DR. FINLAYSON: Let me begin by thanking you for your stamina and hanging in here, and let me tell you what I would first normally do would be repeat the charge that Dr. Goldman has given you, which is that your duty and privilege is to accept

the draft review as written, reject it as written, or modify it and accept the modified version. However, I have been informed by Dr. Smallwood that you do not have a quorum, so we will have to take other steps, so this is for cultural enrichment.

DR. NELSON: Actually, we do. If your talk can be brief, we do, depending on how long you talk.

DR. FINLAYSON: I can make this as brief as you want, and I think I shall make it extraordinarily brief therefore, because much of it is a summary of what is in the packet that you have.

To continue on what we would ordinarily have done was I would give my talk, giving the office overview. Then, Dr. Weinstein would give his talk, giving division overview, and then Dr. Golding would give his talk, giving the laboratory overview, and we would have Dr. Vostal, who is prepared to give his own, because he is a different laboratory from Dr. Golding.

It turns that both Dr. Weinstein and Dr. Golding are out of the country, so I am sorry, folks, you are stuck with me, and I am very good at abbreviating things.

So, let's just run through these slides.

[Slide.]

This is CBER in all its glory, and you see there are lots and lots of boxes, but these boxes that represent offices, there are three product-related offices. This is the Office of Blood Research and Review. That is where we live, and we are going to go down this way here, so if I can have the next one.

[Slide.]

Jay Epstein is the Director, and we are divided up into three divisions: Division of Emerging and Transfusion Transmitted Diseases. You heard from a lot of the folks in that division yesterday. You also heard from Alan Williams both yesterday and today, and Dr. Weinstein, who is not here, is the Division Director of the Division of Hematology.

[Slide.]

The Division of Hematology, in turn, is divided up into laboratories plus a Clinical Review Branch. This is the laboratory that is being reviewed, and Dr. Vostal is in the Laboratory of Cellular Hematology. See, it says Vacant here, meaning that there is not a permanent laboratory

chief, but Dr. Vostal has been serving as the Acting Laboratory Chief ever since the departure of Dr. Liana Harvath.

[Slide.]

This is the breakdown of the Laboratory of Plasma Derivatives, and Dr. Golding has for working purposes divided it up into five informal sections: Immunology I, headed by himself; Immunology II, headed by Dr. Dorothy Scott; Hemoglobin-Based Blood Substitutes, headed by Dr. Abdul Alayash; Safety and Quality Control, headed by Dr. Mei Ying Yu, and Physical Protein Biochemistry, headed by Dr. Andrew Shrake. Dr. Alayash and Dr. Scott were only tangentially involved in the current review because they were reviewed in depth in a previous cycle. So, the principal investigators we are talking about are these three here plus Dr. Vostal.

With your permission, Mr. Chairman, I am going to stop here rather than review the responsibilities of the lab, because they are pretty well spelled out in your package.

DR. NELSON: Okay. Thank you.

Questions?

Dr. Vostal.

Jaro Vostal, M.D., Ph.D.

DR. VOSTAL: Thank you very much for having the opportunity to describe our laboratory.

[Slide.]

Basically, our Laboratory of Cellular Hematology deals with cellular blood products, which is red cells, platelets, granulocytes, and stem cells, and so we look at the safety and efficacy of these cellular products.

We also review the solutions and the devices that are used for their collection and storage, and also some of the products are derived from these cellular products, such as cellular-derived products or platelet substitutes.

Our research is directed at understanding these different cell products, and also in understanding any issues that come up relating to the safety and efficacy of these products. The issue that we are involved in right now is TSE infectivity in blood. We are studying the way that TSE infectivity could be transmitted through blood.

Actually, in the interest of time, I will just skip to my last slide.

[Slide.]

These all deal with prion protein. So, we are trying to figure out how the prion protein

participate in the transmission of TSE infectivity in blood. We are trying to identify which blood cells carry TSE infectivity in rodents. We are using the rodents as a model of TSE infectivity, and we have hampsters and mice, and we are trying to determine if PRPC expression by a blood cell plays a role in TSE infectivity transport, and we are comparing the PRPC expression on human and animal blood cells to evaluate the validity of these animal models, because we think that the expression of a PRPC as the prion protein on different cell types may have a role in the way those cell types can transport infectivity.

Some of these, much to our surprise, some animals, their expression of prion protein on blood cells varies drastically from what is in the human.

There is also a prion protein in plasma and infectivity in plasma, and we are trying to figure out where that prior protein is coming from, is it from the cellular products or blood cells, or is it from endothelial cells.

Finally, we have plans or currently doing, we are evaluating intervention methods, such as leukoreduction or detection methods, such as capillary electrophoresis, and we are trying to

correlate these--this is intervention or detection of prion protein or resistant prion protein--and we are correlating this with TSE infectivity.

In a nutshell, that is our research program in the laboratory.

DR. NELSON: Thank you.

Dr. Smallwood, could we proceed with the closed session?

We are trying to avoid--the issue is that if we don't have a quorum, we will have to have a conference call and discuss the report, and I think it would be preferable not to do that.

DR. SMALLWOOD: At this time, our open session is closed, and we are going now into our official closed session. We will need to ask everyone that is not involved in this session to please leave. We will also need to ask that all of the electronic equipment be closed down with the exception of the transcriber. We hope that you can do this quickly and as quietly as possible.

Thank you.

[Open session adjourned at 4:00 p.m.]

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CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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