U.S. FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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BLOOD PRODUCTS ADVISORY COMMITTEE

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89th MEETING

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FRIDAY,
APRIL 27, 2007

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The meeting convened at 8:00 a.m. at the Hilton Washington D.C. North/Gaithersburg, 620 Perry Parkway, Gaithersburg, Maryland, Frederick P. Siegal, M.D., Chairman, presiding.

COMMITTEE MEMBERS PRESENT:
FREDERICK P. SIEGAL, M.D.
Chairman
JUDITH R. BAKER, M.H.S.A.Consumer Representative
ADRIAN M. DI BISCEGLIE, M.D.Member
WILLARDA V. EDWARDS, M.D., MBA
Member
MAUREEN A. FINNEGAN, M.D.Member
LOUIS M. KATZ, M.D.
Non-Voting Industry Representative
HARVEY G. KLEIN, M.D.Temporary Voting Member
MATTHEW J. KUEHNERT, M.D.Member
COMMITTEE MEMBERS PRESENT (continued):
CATHERINE S. MANNO, M.D.Member
KENRAD E. NELSON, M.D.Temporary Voting Member
GEORGE B. SCHREIBER, Sc.D.Member

SIMONE A. GLYNN, M.D., Msc., M.P.H.Temporary Voting Member
IRMA O.V. SZYMANSKI, M.D.Member
DONNA S. WHITTAKER, Ph.D.Member

FDA PARTICIPANTS:
DONALD W. JEHN, M.S.Executive Secretary
JAY EPSTEIN, M.D.
Director, Office of Blood Research and Review
BASIL GOLDING, M.D.
SHERYL A. KOCHMAN
Chief, Devices Review Branch, DBA/OBRR/CBER
HIRA NAKHASI
MARIA RIOS, Ph.D.
DETTD/OBRR
DOROTHY SCOTT, M.D.
OBRR/CBER
MARK WEINSTEIN, Ph.D.OBRR/CBER
ALAN E. WILLIAMS, Ph.D.Director, Division of Blood Applications, OBRR/CBER

GUEST SPEAKERS:
RICHARD J. BENJAMIN, M.D., Ph.D.Chief Medical Officer, American Red Cross Biomedical Headquarters
CELSO BIANCO, M.D.
America's Blood Centers
EILEEN FARNON, M.D.
Division of Vector-Borne Infectious Disease, Arboviral Disease Branch, CDC
GUEST SPEAKERS: (continued)
JERRY HOLMBERG, Ph.D.Executive Secretary, Advisory Committee on Blood Safety and Availability, DHHS
STEVEN H. KLEINMAN, M.D.University of British Columbia
RAVINDRA SARODE, M.D.Director, Transfusion Medicine and Hemostasis Reference Laboratory, University of Texas Southwestern Medical Center
SUSAN L. STRAMER, Ph.D.Executive Scientific Officer, American Red Cross
DAVID F. STRONCEK, M.D.Chief, Laboratory Services Section, Department of Transfusion

Medicine, Clinical Center, NIH

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C O N T E N T S

P R O C E E D I N G S

DR. SIEGAL: Good morning.

MR. JEHN: Let's everybody sit down and we're getting ready to start. I have a brief statement to read on the conflict of interest, an addendum from yesterday.

This brief announcement is in addition to the conflict of interest statement read at the beginning of the meeting on April 26, and will be a part of the public record for the Blood Products Advisory Committee meeting on April 27, 2007.

This announcement addresses conflicts of interest for the discussions of topic II, Transfusion Related Acute Lung Injury, TRALI, and topic III, issues related to the implementation of blood donor screening for infection with West Nile virus.

For the discussion of Topic Three on West Nile Virus, Dr. Adrian Bisceglie has received a waiver under 18 U.S. Code Section

208(b)(3). A copy of the written waiver may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

Dr. Louis Katz is serving as the industry representative, acting on behalf of all related industry and is employed by the Mississippi Valley Regional Blood Center. He receives consulting fees from firms that could be affected by the discussion.

Dr. Katz is also the medical director for Scott County, Iowa, Health Department, who has a contract with an affected firm. Industry representatives are not special Government employees and do not vote.

The Agency has determined that the information provided by the guest speakers is essential. The following information is being made public to allow the audience to objectively evaluate any presentation and/or comments made by the speakers.

Dr. Richard Benjamin is employed by the American Red Cross. Dr. Benjamin received consulting fees from firms that could be affected by the discussion.

Dr. Celso Bianco is employed by the Americas Blood Centers.

Dr. Eileen Farnon is employed by CDC in Fort Collins, Colorado.

Dr. Steven Kleinman is employed by the University of British Columbia. He receives consulting fees from several firms that could be affected by the discussions.

Dr. Ravindra Sarode is employed by the University of Texas, Southwestern Medical Center. He is a scientific adviser for a firm that could be affected by the discussions, for which he receives a fee.

Dr. Susan Stramer is employed by the American Red Cross. She is the principal investigator on a study from a firm that could be affected. She also was a speaker for an affected firm.

Dr. David Stroncek is employed by the National Heart, Lung and Blood Institute at NIH. As part of his official Government duties, he is a scientific adviser for a NHLBI-funded grant on TRALI.

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

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

Mr. Chair.

DR. SIEGAL: So good morning, it's

Friday, and since it's Friday, I'd like to stick to our time, if we can, so that we can get out at a reasonable hour, unlike yesterday. So I'll try and encourage people to stick to their allotted time.

We're first going to have some committee updates. The first is Jerry Holmberg, executive secretary, Advisory Committee on Blood Safety and Availability, summarizing the August meeting of the DHHS Advisory Committee on Blood Safety and Availability.

Dr. Holmberg.

DR. HOLMBERG: Thank you, Mr. Chairman. Disclosure. I am employed by Health and Human Services and am the senior adviser for Blood Policy and also the executive secretary for the Advisory Committee on Blood Safety and Availability.

Our last meeting was in August, the end of August 2006. We did not have a meeting in January, and at that meeting our

primary topic was whether the United States needed to move towards a biovigilance system. The questions that were asked of the committee were what are the essential components of a basic element of biovigilance? Should biovigilance be considered part of a comprehensive quality standard as expressed by CGMP, CGTP, or CLA? What characteristic--and I should just identify what those are--current good manufacturing practices, current good tissue practices, or the clinical laboratory improvement amendment.

What characteristics of a biovigilance system are already in place within the United States, and also to look at the impact--and I know this is a little difficult to read--Does the U.S. need a biovigilance system? What would be the strengths, weaknesses, opportunities and threats of a biovigilance system? How would a biovigilance system contribute to and

integrate into, with the transformation of the health care system within the United States? And should a biovigilance system integrate with international systems?

In the above questions, how does this integrate, what does this integration mean to the committee as far as standardization of data elements, platforms, data sharing, analysis, and forums to discuss the analysis of the data collected?

We also asked the committee to take a look at responsibilities. What is the responsibility of the Federal Government and the private sector in a biovigilance system? What recommendations, or recommendation or recommendations, does the committee have in regards with the Government's role and function in the development, operation and support of a national biovigilance system?

The committee came back with a recommendation to the assistant secretary, and to the secretary,that the safety of the

U.S. blood supply is a principal activity of the Advisory Committee and the inclusion of efforts to improve organs and other tissue safety and availability also needs to be considered.

We recommend that the secretary coordinate federal actions and programs to support and facilitate biovigilance and partnership with initiatives in the private sector.

The committee also went on to make a definition of biovigilance as a comprehensive and integrated national patient safety program to collect, analyze and report on the outcomes of collection and transfusion and/or transplantation of blood components, and derivative cells, tissues, and organs.

The program should be outcome-driven, with the objective of providing early warning systems of safety issues, exchanging of safety information and promoting education in the application of evidence for practice

improvement.

The committee went on to recommend that there be a formation of an HHS and Public Health Service biovigilance task group for the identification of the vision, goal and process needed to advance these objectives, and the PHS task group should perform several tasks that included a gap analysis, the need for mandatory versus nonmandatory, or regulatory versus nonregulatory reporting, the scope of reporting, database centralization, database governance, format, and standards for data reporting, coordination with non-U.S. safety reporting systems, funding, design, and feasibility of suitable pilot programs.

Since that meeting and since those recommendations were forwarded to my boss, Dr. Aquinobi, there have been several action items.

The first action item was that the Advisory Committee for Blood Safety and

Availability's charter was revised and renewed.

I am pleased to say that Secretary Leavitt signed it the first part of October and as with most of the Advisory Committees, these are under the sunset rules, and so that it has to be reapproved every two years.

The charter was expanded to include the scope of transfusion and transplantation safety. Along with that expansion of the scope of the charter, there was also an expansion of the nonvoting government membership to the committee and that is that we do have representation now from another office within CBER and that is of Cells, Tissues and Gene Therapies, and also within the Health Resources and Services Administration, HRSA, the Department of Transplantation.

There has been a working group formed within HHS operating division and the operating divisions that I'm referring to are

the National Institutes of Health, the FDA, CDC, and CMS, and I'm probably leaving one out but I can't remember, right off the top of my head, to develop a gap analysis, and the co-chairs of that working group are Dr. Kuehnert who is on this committee, and also Dr. Goldsmith from the FDA. I believe that that's all I have for you. If there are any questions, I can take those now.

I apologize for not having a handout available to the committee. This PowerPoint will be available to the executive secretary and if you'd like, copies will be available and will be posted on the Web site.

DR. KUEHNERT: I just wanted to make a quick comment. Just given the discussion we had yesterday about Chagas, I think it's clear that attention to and the coordination of transfusion and transplantation safety issues are missing in the United States somewhat, and we're behind other developed countries in these efforts,

other countries throughout the world already have programs for hemovigilance and, increasingly, biovigilance, to include organ and tissue.

So for us, an integrated platform for surveillance will allow us to catch up, and perhaps lead in these efforts. So we're, at CDC, very excited to be involved.

DR. SIEGAL: Thank you, Dr. Kuehnert.

The next speaker will be Mark Weinstein. Well, it appears, I guess, Dorothy Scott and Mark Weinstein, summarizing the December meetings of the Transmissible Spongiform Encephalopathies Advisory Committee, and FDA's Risk Communication on Plasma Derived factor VIII and Factor XI.

DR. SCOTT: Thank you. On December 15th of 2006, we had a one-day TSA Advisory Committee meeting, and the purpose of that was really threefold. Dr. Anderson, from the Center For Biologics at FDA,

presented the draft quantitative risk assessment for vCJD risk potentially associated with the use of human plasma-derived Factor VIII, manufactured under U.S. license from plasma collected in the U.S., and this was a long time in the making because there were a number of meetings that discussed the inputs to this risk assessment.

It is a highly complex document, and rather than trying to summarize it here without the benefit of Dr. Anderson's presence, I would refer you to the FDA Web site where this risk assessment now is published in its draft form.

At any rate, the risk assessment was presented and it was presented as the amount of potential risk associated with the plasma-derived Factor VIII manufactured as U.S. products.

The additional issues, besides the presentation itself, were the risk communication, which Dr. Weinstein is going

to tell you about, and also a discussion on the experimental clearance of TSE infectivity in plasma-derived Factor VIII products.

So why do we care about the clearance? W ell, obviously clearance of infectious agents is very important in manufacturing processes. It has been shown to be so for viruses, and it's presumed to be so, should TSE infectivity be present in the plasma of donors.

But this risk assessment actually gave us new insight into the impact of clearance. This is something that Dr. Anderson and Hong Yang did called the importance analysis, which is a way of looking at how much the different inputs into the risk assessment make a difference in the outcome, which is a risk in Factor VIII products.

And this is not really numerical but everything is relative here. What you can see, right off the bat, is that the log

of manufacturing reduction of the variant CJD agent has a major impact on risk. That is, the greater the reduction, the lower the risk.

This is compared with some of the other inputs for the risk assessment that are also important but don't reach this level of impact.

Those include the amount of Factor VIII used per year by an individual patient, the prevalence of variant CDJ in the United Kingdom. So the prevalence of variant CJD possibly present in U.S. donors is prorated to that United Kingdom variant CDJ prevalence, and of course it's much lower in the U.S.

The efficiency of transmission of this agent by the intravenous route, which is a real scientific question, the amount of infectivity in human blood of variant CJD, the truth is, we don't have any idea, what that amount is.

What we do know is that there have been reported transfusion transmissions of this agent in the United Kingdom. The quantity of infectivity in blood, we have had to estimate from animal studies of other TSE agents, the yield of Factor VIII from plasma and the efficiency of the donor deferrals that we have to try to limit the number of donors who may have been exposed to bovine spongiform encephalopathy, the agent of human variant CJD.

I'm showing this really, though, to show you this big impact of clearance.

So the amount of clearance by manufacturing processes is a major driver of risk. More clearance; less risk. The TSE Advisory Committee had discussed TSE clearance already on September 19th of last year and in that discussion, they affirm the importance of using bioassays in TSE clearance studies rather than binding assays for the abnormal Prp protein.

And they also discussed the limitations and advantages of the model that we used to study the amount of TSE clearance during manufacturing processes. In particular, they discussed spiking of plasma with a TSE agent, infectious preparation from brain, versus a use of endogenously-infected plasma from animals as starting material for the TSE clearance studies.

However, we asked them in that meeting, would a minimum TSE agent reduction factor, studied by manufacturers in scale-down experiments, enhance the vCJD safety of products? In other words, would the definition of a minimum clearance level enhance the safety?

And we also asked them what TSE agent reduction factor would be appropriate for these products.

The committee at that time had not seen the draft risk assessment and they preferred to respond to these questions

later, when they had also had the chance to review the draft risk assessment and see it presented.

So this all happened in September and that's what brought us to a meeting in December.

I just want to mention a few things about TSE clearance studies. They are done in an analogous fashion to viral safety studies, that is, an infectious agent--and these studies are frequently done and well-defined--the infectious agent is spiked into plasma or the manufacturing intermediate, and then a manufacturing step or series of steps is performed, just as it would be done in the manufacturing facility, and the removal of the infectious agent is assessed at the end of that manufacturing step or steps.

So how much viral clearance does one like to see in a manufacturing process? Well, you obviously want to clear at least the maximum amount of virus that you expect

to be in your starting material, but also it's going to be useful to have a margin of safety, in part, because it's difficult to know exactly how much is the maximum amount of virus in your starting material.

We know what's been published, but we can't be sure, and of course these processes aren't robust, they're not going to remove exactly the same amount of virus every single time because these are complex matrices that are used or that exist as manufacturing intermediates and you cannot control, precisely, every single parameter that goes into precipitation, for example.

You have a range of controls.

So the margin of safety seems like a very good idea. Now how much TSE infectivity do we estimate might be present in plasma? This is the other thing that was important, I think, for the committee to know.

Unfortunately, all of our

estimates are based on animal models, for animals that are infected and the amount of infectivity in their blood or plasma has been measured.

Based on these studies, two to thirty infectious units per mil has been estimated as what is likely or what is present in the plasma of animals, and what we guess might be present in the plasma of people.

And if you take a plasma unit, collected by plasmapheresis, what you find is that you can estimate perhaps 3.2 to 4.4 logs of infectious agents might be present in a plasma unit from somebody who is incubating variant CDJ.

Like many of the inputs to the risk assessment, there are a lot of caveats obviously to this estimate, and you can see this is only one example of many cases where the risk assessment had to take a range of possibilities, based on the best available

data, and use those as inputs for the model. Well, this is the kind of outcome that we got from the model and this is excerpted from a much larger table, which again you can access from Dr. Anderson and Hong Yang's risk assessment that is on the Web.

So this is an example, I'm really showing to you, so that you can see how the levels of clearance impact the real outputs of the risk assessment. In these cases, we're looking at definition of subjects who episodically receive plasma-derived Factor VIII, who do not have inhibitors, so they're not getting super high doses, and with the assumption that the prevalence variant CJD in the United Kingdom, based upon epidemiological modeling, is about 1.8 persons per million.

And very briefly, for 7 to 9 logs range of clearance, the estimate, or the output from the risk assessment is that the risk will be 1 in 3.2 billion to a patient.

If you to 4 to 6 logs of clearance, you have one in 9.4 million.

So you can see that your orders of magnitude differ already, and if you have 2 to 3 logs of clearance, one in 21,500. I'm showing you the point estimate but, actually, ranges were also described in the risk assessment, which is appropriate.

Likewise, these are subjects that again have episodic treatment, no inhibitors, but one estimates the U.K. variant CJD prevalence to be one in 4,225. This estimate is based on a tonsil and appendix tissue survey that was anonomized and done in the United Kingdom to look for evidence of the abnormal prion protein in those issues.

And you can see this number, one in 4,225, is quite a bit different from 1.8 per million people incubating this disease. This is a matter of scientific debate and I think as time goes by and as more surveillance studies are performed, we'll

find out what is actually the case.

And of course these will be asymptomatic people and this number is based on the presence of clinical cases.

So going down, I'm really showing you the same kind of numbers. For 7 to 9 logs of clearance, where you think--this is the U.K. variant CJD prevalence, one in a 100 million, for 4 to 6 logs, one in 105,000, and for 2 to 3 logs, one in 159. So, again, you see, if there's a lot of clearance, there's a very low risk, and if there's quite, a little, or a bit of clearance, there's a substantially higher-looking risk.

I would also like to mention here, that the available data suggests that all of our U.S. licensed products are likely to have TSE clearance of greater than or equal to 4 to 6 logs, based on the studies that we have, using the best available model.

In this session, the manufacturers, through the Plasma Protein

Therapeutics Association, also reported the status of their clearance studies and the kinds of numbers that they are getting in their TSE clearance studies for plasma-derived Factor VIII.

In these studies, they spike the TSE agent into the starting manufacturing material. They use bioassays or binding assays as a readout for TSE infectivity. The types of steps that were generally studied were precipitations, chromatographic steps, and filtrations, and as I said, the U.S. products seemed to have around 4 logs of clearance or more with a series of steps or a number of different steps.

There were varied study designs, and the reason for this is that there are lots of ways to prepare your TSE agent preparation. You can study various numbers of steps, a single step or a sequence of steps, and the readouts were different.

So this is a question we asked the

Advisory Committee, and I'm very nearly finished here, it's a long question, and in fact the committee did us a favor of adding a few things so that they could refine the question.

Based on available scientific knowledge, would a minimum TSE agent reduction factor measure by bioassay, demonstrated using an exogenous spiking model in scaled-down manufacturing experiments, enhance variant CJD safety of the products?

And the committee voted 15 yes and two abstentions.

Then we asked them, if so, what TSE agent reduction factor is most appropriate, and for this they had both the calculation I showed you with how much agent might be present in plasma, in addition to the risk assessment, which suggests the impact of clearance factors and the amount of risk that results, or is estimated.

But the committee, at this time,

did not feel confident in identifying a minimum TSE agent reduction factor, in the main, because they had uncertainties about the current TSE clearance model.

I think the problem here is mainly that we do not have a good idea of exactly what form the agent takes in blood and plasma and so the spiking experiments are a model, the endogenous experiments are another model, but of course you're using animal and not human plasma there, and they didn't feel that they had enough scientific information to be certain that the model used to come up with a reduction factor would be as ideal as possible.

So here I'm going to finish. Thank you for your attention.

DR. SIEGAL: Thank you very much. Are there any questions?

DR. NELSON: You discussed a production process of Factor VIII, but I understand there's been a report from Dr.

Rohr and his group on filtration. Was that discussed at the meeting and how much does that reduce the infectivity? Do you know? Are you familiar with that? Or was that discussed--

DR. SCOTT: Well, I'm familiar with several filtration kinds of steps but I think what you're referring to is a more novel method of filtration, which was not actually discussed at this meeting, because that's sort of an up front filtration for blood or plasma. But it is something that could be very important, certainly, in trying to prevent exposure right at the start. I know that's in development and we look forward to hearing more about it. It's certainly a scientific advance, potentially.

DR. NELSON: What proportion of hemophiliacs get recombinant as opposed to plasma-derived?

DR. SCOTT: I'll probably defer this to Dr. Weinstein. The number that comes

to mind is 80 percent. 80 percent are taking recombinant and about 20 percent are using plasma-derived. The reasons for using plasma-derived, clinical reasons, reasons that people cite, but this does bring up the option, or the concept that there are treatment options for people that they might want to consider in the context of how they feel about the risk assessment.

DR. KLEIN: To my knowledge, there's never been a reported case of CJD in a hemophiliac using Factor VIII. Is that right?

DR. SCOTT: That is correct.

DR. KLEIN: So in the United States, if there's 15- to 20,000 hemophiliacs and the risk is one in a million, even, the chances are that we would never see a case, even if there was a risk of that magnitude, if the majority of the people, as you say, are taking recombinant.

DR. SCOTT: Well, I think that

another point that can be made is so far, there are no known cases in the United Kingdom either, where the exposure was much greater, and up until the late 1990's, when this risk was recognized, they were using United Kingdom plasma for the manufacture of their experiment products.

DR. MANNO: There are some compelling reasons why people still recommend the use of plasma-derived products, although the recombinant products, as we all know, are severalfold more expensive than plasma-derived. Those plasma-derived products that retain von Willebrand factor have specific indications. So I don't know that we've seen the end of plasma-derived recommendations for use.

DR. SCOTT: That's absolutely right, and I should have made that point, that people with von Willebrand disease are essentially obligate users of plasma-derived Factor VIII products.

DR. MANNO: But there are other emerging indications for those Factor VIII products that retain von Willebrand factor.

Your suggestion that they're less likely, when initially used, to be associated with inhibitors--

DR. SCOTT: Inhibitors; yes. And that's certainly another reason--

DR. MANNO: And for immune tolerance therapy, some people would prefer to use plasma-derived products to induce tolerance rather than recombinant product.

DR. SCOTT: Absolutely. Those are two of the other commonly cited reasons for wanting to use plasma-derived Factor VIII. Thank you.

DR. KLEINMAN: Yes. I wanted to ask, in your risk assessment, as incidence figures you use the input of variant CJD risk in the U.K. But I thought you're talking about product that's derived from U.S. sources.

So why didn't you adjust an input calculation to what the risk of a donor in the U.S. for carrying vCJD would be. I assume it would be orders of magnitude lower.

DR. SCOTT: That's quite right, and actually when--it's more complexity than I was thinking of going into for the sake of this presentation, because the full presentation by Dr. Anderson gives you a substantially greater explanation of this.

The way of estimating variant CJD potential prevalence in U.S. donors is to look at the U.K. risk and to estimate how many donors will have been exposed to BSE in the U.K. or in Europe, that might be donating here.

So it is actually prorated. We're not taking the U.K. risk, we're using that U.K. risk to calculate the residual risk in donors in the U.S. So these will be donors that have been in the U.K., or European countries for some time period, below that

time period of deferral, but still may have been exposed. So that's a residual risk and it also includes donors that perhaps ideally should have been deferred but were not deferred because these donor questions are very complex, and you're not going to get a 100 percent perfect deferral.

So that is how that residual risk is calculated and we do show how much risk we think is in the U.K., because we need a starting number to look at the residual risk.

DR. KLEINMAN: So the numbers you put up on the slide were the U.K. numbers--

DR. SCOTT: That is correct. There's pages and pages of calculations about this in the risk assessment, that explain this in substantial detail.

DR. KLEINMAN: Okay. Well, I guess we have interesting bedtime reading, then.

DR. SCOTT: It's a very sophisticated risk assessment, I think,

perhaps the most sophisticated one that's been published for this kind of risk estimate for a TSE agent in blood, and so it is actually very good reading and you can appreciate the complexity and how we had to address the things that we don't have exact numbers for, and that's why we had the two estimates for the U.K. prevalence. But there are many other things along the same line that were done, use of ranges in scientific estimate.

DR. SIEGAL: Thank you very much, Dr. Scott.

The next speaker, Sheryl Kochman, DBA, OBRR, FDA, will summarize the FDA Workshop on Molecular Methods in Immunohematology.

Oh, I'm sorry. We still have Dr. Weinstein. My apologies.

DR. WEINSTEIN: Thank you. Dr. Scott has given you a summary of the discussion that took place at the TSE

Advisory Committee meeting in December regarding the clearance of TSE infectivity from plasma-derived Factor VIII products.

I'll give you an update on our risk communication efforts with respect to variant CJD and U.S. plasma-derived Factor VIII that was presented at that meeting and subsequently modified upon advice from the committee and input from other sources.

I'll also talk about the risk communication regarding an investigational Factor XI product that was made from U.K. donor plasma. Topics that I'll be discussing include the development of key message points in question-and-answer documents, our communications strategy and progress with our Factor XI risk communication.

First of all, with regard to the development of our risk communication messages, the public health messages in the form of key points, and questions and answers, were developed with the input from

our sister Public Health Service agencies, including the NIH and CDC. We also enlisted the help of special Government employees who are patient advocate, as well as experts in risk communication.

The patient advocate SGEs were asked specifically for their comments regarding whether the interpretive documents such as the key points in questions and answers adequately represented the findings of Dr. Anderson's risk assessment.

They were asked whether they felt the documents would be easily understood by the targeted audience and whether they had suggestions to improve the clarity of these documents.

They were also asked whether they had suggestions with regard to how the information was to be delivered to patients and patient family members.

We are extremely appreciative of this input and we feel that the contributions

made a significant difference and improvements in the clarity and delivery of the risk communication messages.

Now we developed three key message points. These encapsulated the major take-home messages with regard to the risk assessment.

The first of these key points summarizes, you know, why we did the study in the first place. I'll just read it off.

In recent years, questions have been raised concerning the risk of variant CJD to hemophiliac A and von Willebrand disease patients who receive U.S.-licensed plasma-derived Factor VIII products.

The second key point summarizes our conclusions with regard to the risk assessment. Based on a risk assessment, the U.S. Public Health Service, including FDA, CDC and NIH, believes that the risk of variant CJD to hemophilia A and von Willebrand disease patients who receive U.S.-

licensed plasma-derived products is most likely to be extremely small, although we do not know the risk with certainty. vCJD risk from other plasma-derived products, including Factor IX, is likely to be as small or smaller.

That latter sentence there is with regard, particularly, to patients with hemophilia B, who we feel would also be interested in this risk assessment.

The third key point gives information about where patients may receive information, further information. Contacting a specialist in hemophilia or von Willebrand disease at a hemophilia treatment enter is a good way to learn about new information as it becomes available.

In other parts of the document, we go into other sources of information, but we felt that the hemophilia treatment center might be the primary source of information.

Now, in addition to the key

message points, we prepared an additional part of this document that gives further information. Again, this slide summarizes some of those key informational, or additional information topics.

We talk about why FDA has conducted the risk assessment, actions that we have taken to reduce the potential of variant CJD, the risk, we talk about the uncertainties in the risk assessment, and again we give suggestions to patients and health care providers about further actions to take and where they can obtain more information.

The last point is that we give current status of the variant CJD risk.

In addition to the key points and additional information document, we prepared another document that is in the form of questions and answers. This is another way of conveying information to interested parties. I'm not going to read all the

questions here that we prepared. They are present in this slide and the following slide. But it gives you a sense of the different topics that were discussed, and of course answers are provide in these documents.

The communications strategy that we had, then, was again to develop these assessments or communication with regard to the risk assessment. We contacted the hemophilia treatment centers, there are about 140 or so in the country. We had a conference call inviting all the hemophilia treatment center medical directors, and other interested parties, to hear about our risk assessment.

They provided input and are willing to disseminate information with regard to this risk assessment.

We also had on that conference call patient advocacy organizations and they are publicizing this risk communication

through their newsletters and other media.

We have done outreach to trade and physicians organizations, and again, the key points in question-and-answer documents list sources for further information and answers to questions. Our primary means of relaying information now is through this Web page that we posted in March of this year. This gives you the address of that Web page, and on that Web page you can find the key points, additional information, the actual risk assessment, and again, we were talking about whether it's good bedtime reading. Well, you can get the full document here, the risk assessment and the appendix, the question-and-answer document. You can also find links to guidance documents regarding donor deferral related to classic CJD and variant CJD, further links to other sources of information including the CDC Web site, and there is a list of patient organizations that people can contact.

The second part of today's discussion includes our Factor XI risk communication efforts.

As you may recall, this has to do with the possible health risk to about 50 individuals who, between 1989, and 2000, received an investigational product, a plasma-derived Factor XI that was made in the U.K. to treat deficiencies of Factor XI.

This plasma-derived Factor XI was made using plasma from donors in the U.K., where variant CJD, where the disease, variant CJD, has occurred.

It's very important to note that the product was not made from the plasma of anyone known to have developed the disease and no one who has received this product is known to have become infected.

However, although the product was not made from plasma of anyone known to have developed the disease, it's still possible that a donor, who felt well at the time of

donation, might have been carrying the disease and so the recipient may have been exposed to--there's a potential of exposure to the recipient of the product.

Our response to this situation is that we also made a computer model of a risk assessment. We reported the preliminary risk assessment results to the TSE Advisory Committee in February 2005, and following the information, received from the committee at that time, and also in October of 2005, we have revised the risk assessment.

The members of the committee also advised the FDA to consult with SGEs, including patient advocates, to obtain input on the risk assessment and communication materials.

So this risk assessment, the preliminary risk assessment was posted on a Web site in 2005. We have subsequently revised that risk assessment and we have finalized communication materials regarding

the risk assessment and have received input from patient advocates and communication experts.

We are now in the process of communicating that information to the individual IND holders, to share information with them, to answer any questions, and we strongly suggested they contact their patients and give them this information. Once this contact has been achieved between the IND holders and the patients, we will be updating our Web page with the finalized risk communication materials and the risk assessment. We will also be contacting hemophilia treatment centers and patient advocacy organizations about this updated Web page. Thank you.

Any questions?

DR. SIEGAL: Well, again, my apologies. Are there any questions?

DR. NELSON: I just wondered whether there's been any update on the data

on the prion prevalence in tonsils and appendices that have been studied, that was going on in the U.K., and that was published some years ago, to try to estimate what proportion of the U.K. population might be carriers. They had just one or two out of 12,000 or something.

I understood that there was an update that hadn't been published. Was that presented at the meeting?

DR. WEINSTEIN: I haven't seen that. MR. ASHER: No.

DR. WEINSTEIN: No. I guess that's David Asher.

DR. SIEGAL: Then let's move on. Thank you. All right. Now we have Dr. Kochman summarizing the Workshop on Molecular Methods in Immunohematology.

MS. KOCHMAN: I'm summarizing a workshop that was held in September of 2006.

It was generously co-sponsored by DHHS, Office of Public Health and Science,

and NHLBI, National Heart, Lung and Blood Institute.

Many would ask why did we need this workshop. There's a growing body of knowledge on the basis of blood group genotypes that's being published in the literature, and we know of growing use of various molecular methods in transfusion medicine.

I should mention that molecular methods have already been widely used in HLA typing and now we're just beginning to see the use being applied to red blood cell antigens.

Tests for IBD use are available in Europe but here, in the United States, it's currently home-grown and research-use-only testing.

These techniques are showing promise of addressing current problems in transfusion medicine. So what are those current problems?

I'm going to go through this pretty quickly. A lack of reagent grade antibodies, both polyclonal and monoclonal. You might think that monoclonal antibiotics would not present a problem, but, in reality, science has been unable to create a monoclonal antibody for every antigen of interest in the red blood cell systems.

There's been variability of reactivity of monoclonal antibodies as compared to each other, as well as the reactivity as compared to polyclonal antibodies, most notably anti D's.

They have varying reactivity with variant D's. We're finding that this is true of other antibodies in the Rh system. We're also noticing weak reactivity of clinically significant antibodies. Most recently, big E and Kel have risen to the list of things that are becoming more difficult to detect.

Jka and Jkb have been consistently difficult to detect. The concern here is

that if there's a failure to detect an antibody to one of these antigens, it may erroneously allow the patient to qualify for the electronic cross-match, thus a serologic cross-match may not be performed to detect incompatibilities, and we are aware of fatalities related to these and other antibodies that we're looking into.

There is also weak expression of the antigen, both on donor and patient cells, as well as reagent red blood cells used to detect those antibodies.

There's a lack of a single universal test method for antibody detection and identification and we know that the different methods are optimum for different antibodies. There is no single method that detects all of the antibodies of interest optimally.

So different transfusion services use different systems, based on what they believe is best for their patient base.

We also know that there are inherent limitations in the human glutination test. There's limited detection on the antibody.

There's clearly a subjective nature of the test performance, reading and interpretation. Proficiency in this area may be a problem.

There are usually single anolytes per test, meaning that you can only test for one antibody or antigen at a time, in general, and we're not always able to automate these serologic methods to allow for mass scale testing.

The goals of the workshop were to provide FDA with sufficient information to frame a dialogue with manufacturers of these kits wishing to proceed to market, to identify potential issues of importance for those manufacturers, and to identify potential issues of importance for users of molecular methods.

Those would be those in blood establishments, transfusion services and reference laboratories.

The agenda is basically reprinted here. It was broken down into the international experience and the Americas experience. From a point of view of the international experience, some of this includes sites in the U.S.

The International Society for Blood Transfusion, and the International Committee on Standardization in Hematology, have provided international workshops and proficiency testing on molecular blood group genotyping.

There was a presentation on a project that is going on in Europe called the BloodGen Project.

There's a great deal of genotyping in Germany, so we had an update on blood group genotyping in Germany and we had a presentation from one of the European

manufacturers on molecular genetic blood group typing by the use of PCR SSP techniques.

For the Americas experience, this sort of includes Canada and South America as well as the United States, there was an overview of molecular methods provided, there was a summary of pheno blood group genotyping, a presentation on the Rh complexities, both serologically and in DNA genotyping, the Kidd blood group system, the Duffy system, the Kell and Kx blood group systems.

A group called the Consortium for Blood Group Genes, CBGG, this is a group of investigators in Canada, the U.S., and South America, who are interested in furthering the use of these methods. They're looking into issues related to standardization, proficiency testing, and that sort of thing.

We had an American company that makes a kit called the Human Erythrocyte

Antigen or HEA B chip, do a presentation. We had a presentation on potential applications of genotype analysis for the quality assurance of reagent red blood cells, applications of blood group antigen expression systems for antibody detection and identification. In other words, is there another way that we can detect antibodies and antigens, then, using red blood cells?

There was a talk on the potential use of donor genotyping. Instead of simply patients, some time spent on proficiency testing for molecular assays and overcoming limitations in current pre-transfusion compatibility testing methods using phage display.

We also presented work on current FDA processes for bringing products such as these to market and a review of the current FDA guidance that applies to molecular testing.

The key points that came out of

the meeting were that using molecular methods in donor screening will allow testing more donors for more antigens, because of automation and multiplex testing.

This will assist in the management of rare donor units. Using molecular methods in patient testing will allow testing when cells are sensitized with antibodies. Right now, in many cases, it's difficult or impossible to do that with serological methods.

Also, it will allow testing when there are multiple cell populations. For example, when a patient has already had one or more transfusions, and clearly, they're going to have cells of different phenotypes circulating.

There are serological methods, they're difficult, they're cumbersome, they're not totally reliable, and so far, the testing is indicating that this method may be useful here, because you can test a sample

other than red blood cells. You can test saliva. You can test epithelial cells.

It's been extremely helpful in resolution of unusual serologic findings, and has been helpful in determining a more rational approach to transfusion practices involving multi-transfused and transfusion-dependent patients.

The focus switches from antibody detection and then transfusion of compatible units to genotyping, and then providing genotype matched or closely-matched units.

We also heard that using molecular methods for fetal genotyping aids in prediction and management of HDN. This has been used in many centers for a number of years now.

Using molecular methods in the manufacture of reagent red blood cells could provide the possible genotype when antisera are not available to determine the phenotype, and that is becoming more and more of a

problem.

And it may also help assist in selection of homozygous cells to increase the chance of detecting weak but clinically significant antibodies, particularly of Jka and Jkb. What we also heard, the molecular methods cannot completely replace serological methods.

Antibody detection and identification currently cannot be done through any molecular methods. There's a strong feeling that we will probably need to confirm the serological phenotype, at least for a while, to confirm that the molecular genotype is giving us the information that we need, and we will need to keep the cross-match, at least for some time, but we don't know for how long.

Some of the concerns that come out when you look at some of the data that were presented, the first ISBT/ICSH workshop in 2004 included testing of a number of DNA

samples. There were 40 participants, six DNA samples.

These samples were tested for about 23 different antigens. There were 34 errors, which was an error rate of 5 percent. I don't know the total number of actual tests in this system or in this particular workshop, but it is clear that there were 34 errors. It calculates out to 5 percent of all samples. Most of those errors were in the Rh system, probably due to its complexity. There were some clerical errors. So molecular methods are not unexpectedly going to help us deal with clerical errors. There was also a failure to detect silencing SNFs, especially for D and DY. So that workshop came away with seven recommendations for use of controls and various testing schemes.

So at the 2005 quality assurance exercise, there were two DNA samples distributed to 29 laboratories, that antigens

covered are listed on the screen. In this case we know there were 496 tests performed. Only three were clearly incorrect results, which brings the error rate down to less than one percent.

So it would appear that some of the recommendations that came out of the first workshop have been extremely helpful in making the testing more reliable.

But there was another workshop in September of 2006, immediately prior to this workshop. Forty-one laboratories participated; six samples were distributed. I don't know the total number of tests. The data that were presented were preliminary.

There were approximately 52 errors at that time, and the percentage of errors is not known. We also heard a lot of details about the BloodGen Project or the gene chip in Europe.

This was a three year project that ended in 2006. Interestingly, it as funded

by a group called the Framework of Five of the EU. They put in 2.5 million Euros and a manufacturing company called Progenica put in 1 million Euros for the study.

They are the company that will be manufacturing the gene chip when it's ready for use.

The major goal of their study is a demonstration project to look for a mechanism for high-throughput molecular testing.

They did include ABO and D in their study, which appears to have been problematic. when they actually went out to do some of the clinical testing, out of 685 samples that were analyzed, 154 of the samples showed a discrepancy between genotype and phenotype.

That's an average error rate of 22.4 percent and the range between the sites was as low as 10.9 percent, which is still awfully high, to as high as 40 percent. They don't know entirely what these errors were

due to.

They're looking into whether or not it was DNA quality issue or whether it's software issue. So software is going to prove to be a huge problem as we go to these methods as well.

So there are some questions remaining, the biggest one being how much premarket testing is needed to evaluate these methods.

The numbers cited for the BloodGen Project are consistent with FDA's draft guidance for field trials, but that guidance was written with serologic methods in mind and has manufacturers using three to 5000 randoms, plus known selected variants for ABO and D, and one thousand randoms plus selected variants for all of the other specificities.

I suspect that that number is not going to be sufficient for molecular testing because there's not the history behind the methodology.

I think we don't know enough about the limitations to adequately inform the user through the package insert. There were problems in the early development and use of monoclonal antibodies and there's a question as to whether or not we can do something to avoid those same kinds of problems.

We need to figure out how the technology should be used. Will this be something that the FDA mandate or will this be something that individual laboratories take on voluntarily.

Will the use in a blood establishment versus a transfusion service versus a reference laboratory be different? Will it be in every transfusion service? Will it be in every blood center?

Should we make it mandatory for manufacturers of reagent red blood cells?

Clearly, we're going to need to educate users in how to perform and interpret the tests and how to recognize when something

needs further investigation, and we need to determine what's going to be the best way to do that.

But did we meet our goals? Partially. We have had discussions with one kit manufacturer. It is clear that proficiency testing will be needed, and it is also clear that tests for some red blood cell antigens are closer to marketing than others.

ABO and Rh are far too complex at this point. I don't see them coming in to the FDA any time soon, whereas the other antigens listed below appear to be much better defined and much closer to market at this time.

And the presenter slides are posted on one CBER Web site and the transcripts for each day are on different Web sites. Both are listed up here. Thank you.

DR. SIEGAL: Okay. Any questions?

[No response]

DR. SIEGAL: All right. Then

let's move on and begin our discussion of TRALI. I hope at the end of these presentations we'll be able to vote on the "rose of Tralee." And we will be able to elect someone.

But we'll start with Alan Williams, PhD, from FDA, to introduce the topic.

DR. WILLIAMS: Good morning and welcome to the discussion on transfusion-related acute lung injury, also known as TRALI.

I'm just going to provide an overview of the session and most of the areas that I'm going to highlight are going to be developed in considerably more depth by the speakers that will follow.

The basic issue for discussion is FDA seeks to be advised whether available scientific data support the development of FDA policies and methods to reduce the incidence of TRALI.

Just very briefly, the TRALI criteria, as focused by a Canadian consensus conference in 2004, clinical criteria defined as acute onset of acute lung injury during or within six hours of transfusion, with clinical evidence of hypoxemia, bilateral infiltrates on a frontal chest radiograph, no evidence of circulatory overload, and importantly, absence of other attributable causes, because acute lung injury itself is not uncommon in the patient population and there are other factors contributing to comorbidity which tends to complicate the diagnosis.

The risk per transfusion of morbidity related to TRALI is estimated to be on the order of one in 2500 to one in 5000 transfused products. Estimates do vary widely, in part, because of the variability in the clinical definition.

TRALI is treatable when recognized with supportive care; however, if not

recognized quickly, it can be fatal and is currently, and has been, for the past three years, the leading cause of post-transfusion fatalities reported to FDA.

Shown here is a table outlining reported fatalities for 2004, 2005, 2006. Focusing on year 2006, there were 35 reported TRALI fatalities, constituting 50.7 percent of all of the reports, followed by hematologic incompatibilities with clinically significant antibodies related to some of the detection problems just defined by Sheryl Kochman.

ABO incompatibility, bacterial contamination, and instances when a clear cause was not identified, the transfusion could not be ruled out, for a total of 69 reported fatalities.

Mechanisms of TRALI will be discussed in detail by Dr. Stroncek, but 45 to 60 percent of cases appear to be associated with neutrophil-specific

antibodies, also known as NSA, in the donor. Donor antibodies to HLA class one or class two antigens also have been implicated, although to a lesser extent, and it's known that these allotypic leukocyte antibodies are stimulated both by pregnancy and transfusion and there will be a talk discussing the prevalence of these antibodies and some of the potential origins.

Of the 2006 reports, the reporting reflects largely a relationship with components that have a high volume of plasma, with 24 of the cases associated with transfusion of fresh frozen plasma. Six cases were associated with red cell transfusion. While there is a low level of plasma contained in intact red cells, this is a little bit aberrant in this particular year because red cells are not typically the component most frequently associated with TRALI.

Two cases were reported with

single donor platelets or plateletpheresis. Two cases with a combination of red cells, NFFP, in one case red cells plus a cryoprecipitate for plasma.

Keep in mind in looking at these numbers, that the denominators vary considerably. Transfusion of plasma occurs, about 4 million transfusions per year, red cells about 14 million per year, and single donor platelets, a little more than 8 million per year.

I believe Dr. Benjamin's going to present some odds ratios for some quite well-characterized data within the Red Cross system, which I think will help elucidate some of the relative risks.

The Blood Products Advisory Committee discussed TRALI, in depth, in June of 2001, and it was I think a very extensive and interesting discussion, but the general consensus of the group was that due to a focused clinical definition of TRALI, and a

real dearth of information regarding the underlying mechanisms that cause it, and the factors in the donors that might be related to development of TRALI, the committee did not recommend regulatory interventions at that time to identify donors or donations with an increased risk for producing TRALI in the recipient by a vote of one yes and thirteen no.

But it sent a strong message, that there was clearly a defined need for increased surveillance, focusing of the clinical definition and production of better data on which to define future interventions.

Importantly, though, following this meeting FDA issued a physician letter to help physicians to understand TRALI, to recognize it and provide the support of care which would help reduce mortality.

And this appears to probably have been quite an important public health measure and I think it clearly increased the amount

of reporting in to FDA leading to an assumption that cases were being recognized on a more reliable basis.

There have been some recent observations regarding TRALI, quite a few of them. The suspected hazards of transfusion analysis in the U.K. and a subsequent intervention study, showed that transfusion incidence was five to sevenfold higher following administration of high-volume plasma units, and in an intervention, the U.K. minimized use of FFP in buffy coat-derived platelets from female donors on the basis that multiparous women tend to have higher levels of allotypic antibodies.

This was done in the fall of 2003, and preliminary reports indicate that the incidence of TRALI in the U.K. has declined dramatically.

There was a consensus conference in 2004 in Canada. This conference introduced standardized TRALI definitions for

TRALI and possible TRALI, and also provided a recommendation that blood collection agencies assess the value and cost of TRALI interventions, and consider implementing interventions to reduce the morbidity and mortality.

Additional observations. A recently published paper by the American Red Cross, which will be presented by Dr. Benjamin today, objectively assessed 550 systemwide probable TRALI cases between 2003 and 2005, found a strong association with plasma administration in 63 percent of the probable TRALI fatalities, and provided odds ratios related to this product.

Plateletpheresis were associated with five of the 38 probable TRALI fatalities or 13 percent. Female donors were disproportionately implicated in development of TRALI, and this publication proposed that limiting plasma from female donors might reduce as many as six recipient deaths

annually in the Red Cross system.

In an association bulletin issued in 2006, the AABB recommended but did not, at this point, make into a standard, interventions related to TRALI, and these interventions that were recommended included that blood collection facilities should implement interventions to minimize the preparation of high plasma volume components from donors known to be leukocyte-alloimmunized or at increased risk of leukocyte-alloimmunization. That blood transfusion facilities should work toward implementing appropriate evidence-based hemotherapy practices in order to minimize unnecessary transfusion.

In other words, clearly, some of these interventions may have an impact on supplies of not only plasma but single donor platelets, and that as well as focusing the interventions to have the best benefit, one should look at the use of the products and

try to optimize that as well, particularly in the plasma arena.

And third, blood collection and transfusion facilities should monitor the incidence of reported TRALI and TRALI-related mortality.

There are some voluntary interventions being discussed and many in fact have already been implemented among the blood collection community. These include, really going back several years now, since the prior BPAC discussion, deferral of donors who have been implicated in previous TRALI cases, preferential use of male plasma for transfusion, selected donor testing for neutrophil-specific and HLA antibodies.

For instance, group AB female donors of plateletpheresis. There's been a focus on review of evidence supporting appropriate use of plasma, and a lot of research has been started regarding mechanisms of TRALI pathogenesis, the

prevalence of associated antibodies and other factors, and the role of previous transfusion in white cell alloimmunization.

So for the agenda for today's discussion, Dr. David Stroncek's going to lead off with an in-depth discussion of clinical and laboratory aspects of TRALI and this will be followed by Dr. Ravindra Sarode. I'm sorry. David Stroncek's with the National Institutes of Health. Dr. Ravindra Sarode is with the University of Texas, Southwestern Medical Center, and he's going to discuss current use of transfusable plasma.

Dr. Steven Kleinman from the University of British Columbia will discuss some very fresh and very useful data derived from the REDS-II LAPS study on HLA and granulocyte antibody prevalence in blood donors, and some of the cofactors.

Dr. Richard Benjamin from American Red Cross will discuss the American Red Cross

experience with TRALI, and Celso Bianco, Dr. Celso Bianco from America's Blood Centers will discuss America's Blood Centers experience with TRALI.

So what we're trying to attain here is not only a scientific review of the field but also a perspective on some of the potential blood supply impacts of potential interventions, and this is an important area for the committee to keep in mind.

Questions for the committee Question one.

Do current scientific data support the concept that the following interventions will reduce the incidence of TRALI?

This includes use of predominantly male plasma for transfusion, the nonuse of plasma for transfusion from donors with a history of prior transfusion, and selective donor screening for anti-neutrophil or anti-HLA antibodies.

And then question two.

Based on the available data, please comment on the effect of the U.S. plasma supply of the following same three interventions. Use of predominantly male plasma for transfusion, nonuse of plasma for transfusion from donors with a history of prior transfusion, and selective donor screening for anti-neutrophil or anti HLA antibodies.

So that's the end of the introduction. I think we have an outstanding set of speakers assembled for the presentations and I look forward to a very informed discussion.

DR. SIEGAL: Are there any questions for Dr. Williams?

[No response]

DR. SIEGAL: All right. Then let's proceed. Dr. Stroncek.

DR. STRONCEK: Thank you. I'm from the Department of Transfusion Medicine at the clinical center at the NIH, and the

views that I express are those of the presenter and they do not necessarily represent the position of the NIH or the Department of Health and Human Services.

And my second disclaimer is that nobody else may have these same views either. TRALI's controversial. So I'm going to go over the definitions of TRALI and the clinical features, and I want to spend some time about what's known about the pathophysiology, including female donors, leukocyte antibodies, leukocyte activating agent, patient factors, and then finally summarize about tests available that people might consider using to screen for donors that would be at risk for causing TRALI.

Again, Alan Williams mentioned this, but TRALI clinically has been defined as severe shortness of breath within four to six hours of transfusion, no signs of fluid overload, and pulmonary infiltrates on chest x-ray.

This definition's been around for quite a while and it was interpreted in different ways by various centers, so some consensus definitions were developed.

As Alan said, there was a Canadian consensus group but there was also an NHLBI group and the NHLBI defined it as TRALI is a new onset of acute lung injury within six hours of the transfusion of a plasma-containing blood product. Again, it shows bilateral pulmonary infiltrates.

They also included a measure of-- again, pulmonary artery preclusion pressure's less than 18, or a lack of evidence of left atrial hypertension. And then they also included a measure of change in the oxygenation of arterial oxygen to inspired O2 ratio of less than three hundred.

And it's difficult to get blood gases but it's much easier to get hemoglobin oxygen saturation by oximetry, so they also included a fall in oxygenation to less than

90 percent done room air. And it's also emphasized that this is a clinical diagnosis. There's no need--it's based on what's happening clinically, it's not dependent on tests for antibodies or other patient tests, donor tests.

The incidence of TRALI is quite variable. It's anywhere from one to a thousand to one to ten thousand units transfused. I think some of the more recent studies that have looked at this more closely have found the incidence is more closer to one to a thousand transfusions than one to ten thousand.

Again, all blood products have been implicated but plasma-containing products such as FFP and platelets tend to be more commonly involved with TRALI.

What is interesting is it's been reported that solvent detergent plasma does not cause TRALI. Several years ago, solvent detergent plasma was developed and this is

made from pooled plasma, and was used in the United States for a while, and it's still used in a few places in Europe, and the places where it's being used have been reported, that it's not associated with TRALI. It's not sure why this is but it's speculated that the pooling of the plasma dilutes out any leukocyte antibodies present in the plasma.

Again, the clinical features. The patients usually become dyspneic and hypoxic during the transfusion or shortly afterwards. They may experience fever. They often become either hypotensive or hypertensive, and then the x-ray showed bilateral pulmonary infiltrates. On occasion, an x-ray will show a whiteout type picture.

Treatment is usually just supplemental treatment with oxygen therapy. A number of these patients required intubation and mechanical ventilation. If they're hypotensive, they made need

intravenous fluids or agents to increase blood pressure, often because acute lung injury is often treated with corticosteroids.

These patients are given steroids. It's not clear if that makes any difference.

Typically, the symptoms resolve with 24 to 48 hours, so usually with supportive care, this resolves fairly quickly. Sometimes the symptoms will even resolve before the diagnosis is fully established. But despite that, the mortality rate of this syndrome is really pretty high.

It's been reported to be anywhere from 10 to 50 percent. So it remains a serious problem. So now a couple minutes on the pathophysiology.

You've heard that a number of centers are excluding females from donating plasma for transfusion, and why the concern for female, about female donors originally. And this study is about five years old now and it's from a Scandinavian group.

But this is a prospective, randomized study of plasma from multiparous donors compared to control donors. So they had a 100 ICU patients and they randomized them into two groups. One group got control donor plasma first, followed a couple hours later by a unit of plasma from a multiparous female.

The second group was randomized the other way, to get the multiparous donor plasma first, followed in a couple hours by control donor plasma.

After each transfusion, blood gases were measured as well as blood pressure, heart rate, temperature, and then they compared. So they were comparing the effects of the control plasma versus multiparous plasma on these variables, and what they found is on blood gases, you'd expect the control plasma, it really shouldn't do anything to oxygenation, and the arterial oxygen to FIO2 ratio didn't change

with control plasma.

However, with multiparous plasma, the oxygenation fell and this suggests that again the multiparous plasma was causing some pulmonary dysfunction.

Similarly, you'd expect with a plasma infusion you'd get some volume expansion and blood pressure increase, and with the control plasma that was the case. The mean arterial pressure increased slightly, but that wasn't the case with multiparous plasma.

So this data suggests there is something different about multiparous plasma that causes some cardiopulmonary problems. Unfortunately, this group didn't test all the donors for leukocyte antibodies, so it's unclear what caused this. What they did do, though, is they noted transfusion reactions, and out of these 100 patients, there's one case of TRALI and that case was associated with a transfusion of a multiparous donor FFP

unit.

They tested that unit for leukocyte antibodies and a granulocyte antibody was found but no HLA antibodies. So this does support that granulocyte antibodies can cause TRALI.

They also had four mild reactions. One was just a febrile reaction and that was from a control unit. They had three pulmonary reactions. They didn't meet the criteria for TRALI but the patients did have some shortness of breath.

All three of those units were associated with multiparous donors and one of the three units had a granulocyte antibody but not HLA antibodies were detected in the units.

There's been a recent study from the Mayo Clinic that looked at TRALI in intensive care unit patients, and this again suggests a role for plasma-rich products. Again, this is a single institution

retrospective case-controlled study.

What they did is in some of their intensive care units, they looked at all the new cases of respiratory failure within six hours of a transfusion. They identified 24 TRALI cases, 25 cases of fluid overload. Then they took and matched, found matched patients in the intensive care unit and they identified 124 of those patients, and they compared the transfusions in the patients with TRALI and the controls, and they found that TRALI patients were more likely to get plasma-rich products and they did an estimate of the volume of plasma they were infused, and the TRALI patients had larger volumes of plasma.

These were the primary end points. So then they looked at secondary end points, which would be looking at how many of the plasma donors were female donors, and they had a higher incidence of female plasma donors in the TRALI group. But as they

pointed out, that study really wasn't designed to test this issue. So this is a hypothesis-generating finding and further study should be undertaken for that.

Okay. So there's some other studies that point out that female donor plasma may be bad but some of the other presenters will go over those, so I won't mention those. What about specific causes of what people have found that cause TRALI?

I first want to go over the data that supports the role for leukocyte antibodies in TRALI, and this issue goes back to the 1950's, and the first real case of, really a good case of TRALI in leukocyte antibodies was reported in 1957, and Brittingham was studying the effects of alloimmunization in blood transfusion, and they infused subjects, three subjects with plasma from--plasma that had leukoagglutinins in. In one patient, they infused 50 mls of blood and they stopped the transfusion. This

blood with leukoagglutinins caused vomiting, diarrhea, chills, fever, hypertension, tachypnea, dyspnea, cyanosis and leukopenia within 45 minutes.

These are classic symptoms of what we know cause TRALI. The symptoms resolved the next day but they did a chest x-ray and it showed bilateral pulmonary infiltrates and a small pleural effusion and they resolved by two days. So really a classic case of TRALI.

I only mention that. In this report, they also transfused two other patients with 250 mls of plasma containing a weaker leukoagglutinin and these patients didn't have reactions.

So, again, not all leukocyte antibodies cause transfusion reactions.

At this time, they had identified leukoagglutinins but they didn't know what they were. These have been described as HLA antibodies and neutrophil-specific antibodies.

Neutrophil-specific antibodies that have been reported to cause TRALI include human neutrophil antigen I, II and III, and both HLA class I and class II antibodies have been associated with TRALI.

Again, in the '60s and '70s, there are several case reports of TRALI associated with the transfusion of leukoagglutinins, but you have to remember about case reports--and this is well-summarized by Thompson in 1971--that our case reports suggest that acute pulmonary edema was related to leukoagglutinins but such a relationship was not established, and interestingly enough, in 1971, they were suggesting that we should avoid transfusing plasma from multiparous donors.

In the 1980's, the idea that leukocyte antibodies causes TRALI was firmly established and a definition of TRALI was, at least the clinical definition we've been using for many years, was by Popovsky and

Moore, and they reported five cases of transfusion reactions or TRALI in 19 implicated donors, and one donor in each case had an HLA antibody.

They had another case of more patients, two years later. They described 36 cases. They found leukocyte antibodies in 89 percent of, at least in one donor from 89 percent of the cases, and HLA antibodies in 65 percent.

So this is interesting but they're not controlled studies, and what you have to remember is oftentimes a patient that's getting transfused, they may not just get one product, they may get two red cells, for example, four units of FFP and one unit of platelets.

And the incidence of HLA antibodies in any one blood donor has been reported to be 4 to 7 percent. So if you get transfused with 6 or 7 units, just by chance, there may be 20 to 30 percent of the donors

may have HLA antibodies.

So it's really very difficult to interpret what it means to find HLA antibodies in units of blood that cause TRALI, without having a control group, and with neutrophil antibodies it's a little different, because a number of studies have found that less than one percent of blood donors, or even about .1 percent of blood donors have neutrophil antibodies.

So if a neutrophil antibody is found in one of these units, it's more suggestive that it is causing TRALI. That said, there is evidence that leukocyte antibodies can cause, does cause TRALI, and there's been a number of reports of the transfusion of both HLA neutrophil antibodies associated with TRALI and leukopenia, and if you're transfusing an antibody and it's caused leukopenia, and then have a transfusion reaction, it's very suggestive that these are all related.

One case of transfusion of neutrophil antibody to antigen 1B was reported by Yomtovian in 1984. And then there have been three cases of the transfusion of HLA class I and II antibodies causing leukopenia and TRALI, followed by another group of three cases of the transfusion of HLA antibodies causing leukopenia and TRALI.

Dr. Fadeyi, in our group, has found that the transfusion of a neutrophil antibody, HNA-2a, causes leukopenia and pulmonary symptoms, shortness of breath, but not TRALI.

So there's good evidence that these are all suggestive, that it's not a good thing for the lungs to transfuse leukocyte antibodies.

There's been some look-back studies, much like the infectious disease literature, where, if a unit, a donor's blood is implicated in TRALI and you find they have

an HLA antibody, you'll go back and look at the previous transfusions and see how many have been associated with TRALI, and Akopko reported that antibodies to the neutrophil antigen 3a frequently caused TRALI.

They had one donor who was involved with 36 previous transfusions. Fifteen of those caused at least a reaction and eight of those were severe, really pretty severe TRALI. So that suggests that this leukocyte antibody was pretty potent in causing a pulmonary reaction.

Another group had an antibody with the same specificity from one donor who donated 25 times, but they didn't see any reaction. Again, Fadeyi had an antibody to neutrophil antigen 2a, that donor donated 39 times, twelve were associated with reactions, but they were more mild and none with TRALI.

In contrast, with HLA, antibodies to HAL class I and II antigens, there have been four reports. The only one that really

has found TRALI, of these approximately 140 units, was a report by Pearl Toy, they had one reaction and it was TRALI. So it looks like the HLA antibodies are slightly less potent in causing transfusion reactions than neutrophil antibodies.

There's been a recent report in Vox Sanguinis that supports this. This is a group in Poland that looked at a thousand blood donors. They looked at 633 were previously pregnant women, 410 were male, they tested them all for HLA neutrophil antibodies. No neutrophil antibodies were detected in any of these thousand donors. No HAL antibodies were tested, or found in the males. HLA antibodies were found in 9.8 percent of the females.

They then went back and looked at approximately 60 females who had HLA antibodies and they had donated 211 components, and they found of these components, one of them was associated with

TRALI and that was a red cell from a woman with multispecific antibodies to HLA class I and class II antigen.

Again, about one in 200 units with HLA antibodies was associated with TRALI, which is higher than about the one in a thousand to one in ten thousand incidence reported from any unit.

Finally, there's animal models that are associated with transfusion of neutrophil antibodies and HLA antibodies with pulmonary injury that is similar to TRALI, and all of these models require not only the antibody but neutrophils must be present, and one of them requires that complement must be present.

So what about other factors people have implicated in TRALI? One is Silliman, from Denver, has done a lot of work with bioactive lipids. These are lipids that accumulate in blood products during the storage of cellular blood products.

What they do is they prime neutrophils. So what do we mean by priming? Is that prime neutrophils, they don't really do anything on their own until they're stimulated with an activating agent, and when they're primed, the response to the activating agent is greater than if a nonprime neutrophil is stimulated, and they've that these prime new factors, specifically the bioactive lipids, they're given to animals before an insult, that they will enhance neutrophil-mediated lung injury.

And then they went on to do clinical studies, and there's been prospective and retrospective studies that found a greater level of bioactive lipids in TRALI-implicated units or post-transfusion sera from TRALI patients, when they compare these with controls.

Again, these have been small studies and they've been typically single institution studies.

Similar, recently, a soluble CD40 ligand has been implicated in TRALI. It's been found that soluble CD40 ligand is released by platelets during storage. This is also a neutrophil priming agent.

A number of animal models have shown that CD40 and CD40 ligand system incudes acute lung injury in animals, and in this particular study published in Blood, there was a case control study where they compared soluble CD40 ligand levels in units that were implicated in TRALI with control units, and there were higher levels in the TRALI-implicated units. Again, this was a single institution study with a relatively small number of patients involved.

Patient factors have also been reported to influence transfusion, TRALI, and Brenda Moore anecdotally reports that he sees more of it at the Mayo Clinic in surgery patients, and Silliman gain had a case control study where they looked at TRALI, and

they found TRALI was more likely to occur in hematological patients, patients with hematological malignancies or patients with cardiac disease.

So the fact that there's multiple factors that have been implemented in TRALI has led to a so-called "two hit model" for TRALI, and in this model, patient conditions are thought to lead to the activation of pulmonary infiltrates, which leads to sequestration of neutrophils in the lungs.

When these neutrophils are stuck on the endothelium in the lungs, they become prime, and then infusion of a leukocyte antibody or a CD40 ligand, or a bioactive lipid, then stimulates these prime neutrophils and they cause pulmonary damage, capillary leak, and pulmonary edema and TRALI.

Finally, I want to conclude with a few minutes on possible testing and issues associated with that for TRALI, and what are

the types of things you might want to test for to eliminate TRALI would be HLA antibodies, neutrophil antibodies, bioactive lipids or CD40 ligand. Testing for antibodies would be fairly straightforward, just like we test or many viruses now.

We test donor serum and we test them at the time of donation. Testing for bioactive lipids in CD40 ligands is not the same.

Because they accumulate during storage, we'd have to test the product and they'd be tested at the time of transfusion. So that makes that a little more complicated.

The other issue is for HLA antibodies the techniques are well-established. There's solid phase assays to do it and they're commercially available. Testing for neutrophil antibodies is more difficult. These assays require intact neutrophils and no commercial kits are