UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

BLOOD PRODUCTS ADVISORY COMMITTEE

81ST MEETING

THURSDAY, OCTOBER 21, 2004

The meeting came to order at 8:00 a.m. in the Ballroom of the Gaithersburg Holiday In,, 2 Montgomery Village Ave, Gaithersburg, MD 20877, James R. Allen, Acting Chairman, Presiding.

Present:

James R. Allen, M.D., M.P.H., Acting Chairman
Kenneth Davis, Jr. M.D., Member
Samuel H. Doppelt, M.D., Member
Harvey G. Klein, M.D., Member
Judy F. Lew, M.D., Member
Charlotte Cunningham-Rundles, M.D., Ph.D., Temporary Voting Member
Jonathan C. Goldsmith, M.D., Temporary Voting Member
Liana Harvath, Ph.D., Temporary Voting Member
Blaine F. Hollinger, M.D., Temporary Voting Member
Matthew J. Kuehnert, M.D., Temporary Voting Member
Kenrad E. Nelson, M.D., Temporary Voting Member
Keith C. Quirolo, M.D., Temporary Voting Member
George B. Schreiber, Sc.D., Temporary Voting Member
Michael D. Strong, Ph.D., Non-voting Industry Representative
Linda A. Smallwood, Ph.D., Executive Secretary

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

8:05 a.m.

DR. SMALLWOOD: On the record. Good morning. Welcome to the 81st meeting of the Blood Products Advisory Committee. I am Linda Smallwood, the Executive Secretary. At this time, I will read the Conflict of Interest Statement that applies to the proceedings for this meeting over two days.

This announcement is part of the public record for the Blood Products Advisory Committee Meeting on October 21, 22, 2004. Pursuant to the authority granted under the Committee charter, the Director of FDA Center for Biologic Evaluation and Research has appointed the following individuals as temporary voting members: Drs. Charlotte Cunningham-Rundles, Jonathan Goldsmith, Liana Harvath, Blaine Hollinger, Matthew Kuehnert, Kenrad Nelson, Keith Quirolo and George Schreiber.

To determine if any conflicts of interests existed, the Agency reviewed the agenda and all relevant financial interests reported by the meeting participants. The Food and Drug Administration has prepared general matter waivers for the special government employees participating in this meeting who required a waiver under Title 18, United States Code

208.

Because general topics impact on so many entities, it is not prudent to recite all potential conflicts of interests as they apply to each member. FDA acknowledges that there may be potential conflicts of interests but because of the general nature of the discussions before the Committee, these potential conflicts are mitigated.

We would like to note for the record that Dr. Michael Strong is participating in this meeting as the Non-voting Industry Representative acting on behalf of regulated industry. Dr. Strong's appointment is not subject to Title 18, United States Code 208. He is employed by the Puget-Sound Blood Center and Program and thus has a financial interest in his employer.

He also is a researcher and a speaker for a firm that could be effected by the Committee discussions. In addition in the interest of fairness, FDA is disclosing that his employer, Puget-Sound Blood Center has associations with regional hospitals and medical centers.

With regard to FDA's invited guest speakers, the Agency has determined that the services of these guest speakers are essential. There are

interests that are being made public to allow meeting participants to objectively evaluate any presentation and/or comments made by the guest.

For the discussions of Topic 1 related to Reentry of Donors Previously Deferred for Anti-Hepatitis B Core Reactivity, Dr. Susan Stramer is employed by the American Red Cross.

For the discussions of Topic 2 related to The Simian Foamy Virus, Drs. James Brooks and Peter Gantz are both employed by the Biologic and Genetic Therapies Directorate, Health Products and Food Branch, Health Canada. Dr. Walid Heneine is employed by the Division of AIDS Research at the Center for Disease Control. Dr. Nicholas Lerche is employed by the California National Primate Research Center, University of California.

For discussions of Topic 3 on Deferral on Donors with Possible West Nile Virus, Dr. Michael Busch is employed by the Blood Centers of the Pacific. He has contracts and is a researcher, speaker and advisor for firms that could be effected by the discussions. Dr. Theresa Smith is employed by the National Center for Infectious Diseases, Center for Disease Control in Fort Collins, Colorado. Dr. Susan Stramer is employed by the American Red Cross.

In addition, there are regulated industry and other outside organization speakers making presentations. These speakers have financial interest associated with their employer and with other regulated firms. They were not screened for these conflicts of interests.

FDA members are aware of the need to exclude themselves from the discussions involving in specific products or firms for which they have not been screened for conflicts of interests. Their exclusion will be noted for the public record.

With respect to all other meeting participants, we ask in the interest of fairness that you state your name, affiliation and address and any current or previous financial involvement with any firm whose products you wish to comment upon. Waivers are available by written request under the Freedom of Information Act. At this time if there are any additional declarations to be made by anyone involved, please do so.

Hearing none, I will move to my next series of announcements. First, I would like to announce that Dr. Jay Epstein, the Director of the Office of Research for Blood, is delayed because of an accident on his way in. So we will proceed with the

meeting. However once he arrives, we will make adjustments with respect to acknowledgment of our outgoing members.

So at this time, I would just like to make a few announcements and I will then turn the meeting over to our chairman. On the table outside, there was an announcement of a notice of the Second Annual Stakeholder Meeting on the Implementation of the Medical Device Userfee and Modernization Act. That meeting is to take place on November 18, 2004. So if you would please be advised of that and there is this copy that is out on the table.

Secondly, I would like to give you the tentative meeting dates for the Blood Products Advisory Committee for 2005. They are as follows: March 17 and 18, July 21 and 22, December 1 and 2. Again these are tentative and you will be advised in the appropriate fashion.

At this time, I would like to introduce to you the members of the Blood Products Advisory Committee. As I call your name, would you please raise your hand. For this meeting, the Acting Chairman is Dr. James Allen. Seated next to him is Dr. Liana Harvath, Dr. Kenrad Nelson, Dr. Matthew Kuehnert, Dr. Keith Quirolo, Dr. Blaine Hollinger, Dr.

Jonathan Goldsmith, Dr. George Schreiber, Dr. Michael Strong, Dr. Judy Lew, Dr. Harvey Klein, Dr. Samuel Doppelt and Dr. Kenneth Davis. Dr. Allen.

ACTING CHAIRMAN ALLEN: Good morning. I would like to welcome you all to the Blood Products Advisory Committee Meeting. We have, I think, a very important agenda before us over the next two days. We'll start out with some Committee updates. I would like to remind all of the speakers please that it is important to keep to the time limits that have been assigned to you during the presentations.

Also I just would like to remind speakers that you have a diversity of backgrounds of people on the Committee. I think everybody here is expert. Together we make a remarkable committee. We do not all have expertise in all the jargon of each of the fields that are necessarily being presented. So to assist in our fully understanding what you're saying, it would be helpful as you first begin talking about a topic if you're using jargon or abbreviations or acronyms and so on, please provide explication for the Committee about that term.

We'll move forward. The first update is a summary from the meeting last week of the Transmissible Spongiform Encephalopathies Advisory

Committee (TSEAC) to the FDA. Dr. Asher.

DR. ASHER: Thank you. Good morning. I'm going to present my own informal summary of part of last week's TSE Advisory Committee's meeting. With the exception of one statement that will be obvious, the rest of the talk is my own informal summary. There's a formal summary out on the table kindly prepared by Bill Freas, the Executive of the Committee. And within two weeks, we should have posted on the web the transcripts, all the Government presentation slide sets and most of the non-government presentation sets for your use.

The Committee heard five informational presentations that I won't summarize and then the sixth issues was decisional and that is one of periodic reviews of our FDA/CJD, vCJD Blood Safety Policy. The Committee was asked to reappraise the adequacy of current policies. We began with a history of FDA actions, then the recent events of concern which I'll go over in just a minute and then we had a full scientific program addressing the blood policies and then questions for the Committee. Next please.

The Committee, the formal charge was to provide advice on whether recent information regarding Variant Creutzfeld-Jakob Disease (vCJD) warrants

consideration of additional safeguards for FDA regulated human blood and blood products. Next please.

Actually the history of FDA policy goes back to 1983 which was the first time that the FDA announced policy based on the assumption that human blood was likely to be similar to animal blood in that it would be infectious during both the incubation period and clinical disease of Spongiform Encephalopathies.

The first geographic based deferral policy was recommended in 1999, deferral of donors who had spent six months in the United Kingdom between the beginning of 1980, the presumptive start of the BSE outbreak there and then end of the 1996 when the U.K. had implemented a full set of strict food chain protections. Current policy was announced in January of 2002.

In December of 2003, U.K. authorities reported the first case of vCJD occurring in a small cohort of recipients of labile blood components, one of the 50 such recipients in only 15 to survive underlying disease for more than three years. In July of this year, the United Kingdom reported a second transfusion associated case.

In the same month from the U.K. came a survey of appendicle tissues from an anonymous operating room specimens and it found this as I'll show you in a few minutes a surprising high number of those tissues contained abnormal protease resistant prion protein thought to be a finding years before the onset of neurological disease.

Then finally, an issue of concern to many people in September of this year, the United Kingdom authorities notified certain recipients of plasma derivatives that they were at increased risk for variant Creutzfeld-Jakob disease.

In conjunction with that although referred to indirectly at the TSE Advisory Committee, I'd like to read to this Committee a statement from CBER. "U.K. authorities recently notified some recipients of plasma derivatives that they might be at increased risk of vCJD. These products included Coagulation Factors 8, 9 and 11 as well as Anti-Thrombin 3 and intravenous immunoglobulins. The derivatives of concern were manufactured from plasma of U.K. donors between 1980 and late in 1999 when consistent with a decision announced in 1998, U.K. manufacturers stopped using U.K. plasma. The last expiry date for any of the U.K. products was in 2001.

Some Factor 11 made from U.K. plasma was used between 1989 and 1997 to treat a relatively small number of patients participating in several investigational new drug studies in the United States. No Factor 11 product used in the United States was manufactured from a pool containing plasma from any donor known to have become ill with Variant Creutzfeld-Jakob Disease. That is there were no known implicated lots. The FDA and CDC are discussing the Factor 11 importations and assessing the risk to recipients. This assessment will be the basis for any further recommendations."

I think it's fair to say that this issue which was not on the agenda of the TSE Advisory Committee is of sufficient significance that one can expect that it will be addressed more fully in subsequent meetings of the TSE Advisory Committee. Next slide please.

I summarize in the handout current U.S. blood donor policies and there are policies regarding both donor at increased risk for conventional forms of Creutzfeld-Jakob Disease and Variant Creutzfeld-Jakob Disease. Next slide please and move on to the next slide.

There's a greater concern about Variant

Creutzfeld-Jakob Disease because it's so very different from other forms of Creutzfeld-Jakob Disease, both in its neuro-pathology and in other pathology. There are accumulations of abnormal prion protein in lymphoid tissues that are not seen in other forms of Creutzfeld-Jakob Disease. Next slide please.

For that reason, we were concerned that because of this unusual involvement of lymphoid tissues there was a greater likelihood that there might be infectivity in blood. In a general way because the disease was so different in clinical presentation and in pathology, there was uncertainty about how predictive the relatively reassuring epidemiological information that suggested that if actual transmissions of conventional CJD had occurred through blood, we wondered whether we could rely on that evidence to predict the behavior of vCJD. For that reason, more strict policies were recommended. Then of course, when the U.K. authorities announced their own lack of confidence serum of U.K. origin, it had to increase our own concern. Next slide please.

There is some good news. Throughout the world, the 23 known BSE countries, the recognized cases of the disease are decreasing in most of those countries with the exception of Spain and the

possibility of one other country. Next slide please.

In the U.K. where the disease peaked at tens of thousands of cases in cattle, in 1992 only 600 cases were recognized last year. Also good news, over 80,000 cows in risk groups have been tested since June by the U.S. Department of Agriculture and although the surveyance program may not be perfect, it has to be reassuring that not a single true positive brain has been detected in that survey nor have any brains been detected in a smaller survey conducted in Canada. Next slide please.

The number of cases of vCJD worldwide is smaller than some had feared at the beginning of the outbreak. One hundred and sixty cases have been recognized as of earlier this month. One hundred and forty-nine of them have been in the U.K. and three in long time residents who moved to other countries. However, seven cases in France and one case in Italy occurred in people who had never visited the United Kingdom. Next slide please.

There is also good news from the United Kingdom in that new cases of vCJD appeared to have peaked in 1999 and deaths in 2000. Next slide please.

The cases of vCJD in U.K. residents have permitted some projection about what the minimum

incubation period of the disease might be. A minimum of nine to 11 years incubation is concluded from the U.S. and Canadian case.

The Irish case had a history that traveled back and forth. So it's hard to draw any conclusion from that case. The blood borne cases that I'm going to present now suggest that there's an incubation period of six years in one case and greater than five years in a second case who had not developed symptomatic disease. Next slide please.

Not such good news is a finding of an appendicle survey that was published in July of this year. This is based on the recognition at autopsy that most patient with vCJD had detectable prion protein in lymphoid tissue and then fortuitously, two of the cases had had operations on tonsils and appendix done several years before they died which demonstrated that the abnormal protein was detectable in tonsils and appendix for at least two years before death, but not ten years before death.

That was the basis of a survey of normal tonsils and appendix that I just referred to. The tonsular survey didn't turn up anything, but the appendix based survey found three positive appendices out of 12,674 adequate specimens which predicted a

probable rate in the population of more than 100. Two hundred thirty-seven was their actual predication cases of incubating vCJD per million population which is somewhat discordant from the mathematically-based projections, but it certainly is of concern and shows you the uncertainty surrounding the whole situation. Next slide please.

As most of you know, the first probable transfusion transmitted case of vCJD in the U.K. was recognized last year. A clinically healthy blood donor became ill with vCJD three years after the donation and a recipient became demented and died with vCJD three years after that. Next slide please.

The second case was reported in July of this year. The donor became ill 18 months after donating whole blood in 1999. Both these recipients by the way received non-leukoreduced red blood cell concentrates. The recipient died of a ruptured aortic aneurism without any history of dementia. It's interesting that the tonsils and appendix of that recipient were normal but abnormal prion protein was present in several areas of the spleen and in cervical lymph node. There was really very little doubt that the recipient was incubating Creutzfeld-Jakob Disease and judging from the behavior of these infections in

animals, one would think that within a couple of years the patient would probably have come down, the infection would have entered the central nervous system, the patient would have come down with Creutzfeld-Jakob Disease.

One unfortunate interesting observation of this patient, this is the first patient studied found to be heterozygous for methionine and valine at Codon 129 of the prion protein and coding gene. The heterozygous genotype is known to be somewhat but not completely protective against other forms of Creutzfeld-Jakob Disease, Sporadaica Creutzfeld-Jakob Disease, Iatrogenic Creutzfeld-Jakob Disease and some had hoped that it would be completely protective against Variant Creutzfeld-Jakob Disease. Clearly, that is not the case. Next slide please.

So the implications for public health of these findings I've listed here. CJD was transmitted by transfusion. I think the only logical, the chances that these are two fortuitous dietary acquired cases occurring in a cohort of 15 people who survived for more than three years is less than one in a billion. So I think the only logical conclusion is that these were transfusion transmitted cases. Although there's nothing like genotyping that one can do to establish

the connection at a molecular level.

The prion protein, methioline and valine 129 genotype did not convey absolute resistance to infection at least after adaptation to humans and intravenous exposure. A second wave of vCJD cases in heterozygous individuals is possible, possibly smaller than the first wave and of unknown magnitude. That's because 50 percent of the U.K. population is heterozygous for that gene, for methioline and valine at that gene.

A recent survey of prion protein in appendix predicted a rate of 237 infected people per million in the U.K. That has to be considered a minimum rate if it's confirmed. A number of persons in the U.K. and other BSE countries potentially have vCJD in their blood and that can be present for at least three years prior to the onset of clinical disease. For that reason, we continue to believe that BSE geographic-based blood donor deferral policies have been prudent and remain justifiable. Next slide please.

We put to the Committee no specific options although Peter Gantz who I think will be here this afternoon laid out the three options that Canada is addressing, one of which is through keep current

policies and the other two we'll discuss now. There are really only a limited number of ways in which risk can be reduced further.

The policies are based on reducing the risk that a donor has been exposed to the BSE agent either in food or through pharmaceuticals. We've had to take residence in a BSE country as a surrogate for food exposure because dietary histories are considered quite unreliable.

The only other exposure of concern has been bovine insulin. That's already part of the deferral policy. There's no comparable bovine product that was made either in the U.K. or in any other BSE country that we're aware of. So that one approach would be to reduce the time that an acceptable donor might have spent in a BSE country or to add new lower risk BSE countries to the list of countries for which there is deferral.

The second strategy would be to reduce the risk that the donor had been exposed to vCJD agent from a human exposure and in 2002, we recommended deferral for anyone who had been transfused in the United Kingdom after 1980. One might consider deferrals for transfusions received in other countries. The Committee itself suggested that we

might consider similar deferrals for people who had surgery in BSE country although that remains a theoretical risk whereas the transfusion transmission is now a demonstrated risk. Next slide please.

To help the Committee in their deliberations, there were a number of very useful talks. Robert Will summarized the situation that I just summarized for you. Steve Anderson compared the risk of classic and vCJD. Peter Page, I think, is here this morning presented the American Red Cross Lookback Study of recipients of labile components here in the United States, one hundred and sixteen recipients living more than five years without a single case of Creutzfeld-Jakob Disease.

Steve Anderson did a Fisher Exact Test and it's a highly significant difference. The pathogenesis of the two diseases in regard to their transmissibility by blood appears to significantly different. Louisa Gregori from Bob Roars' lab in Baltimore presented very interesting results of their studies with one leukoreduction filter and found that although about 40 percent of hamster blood infectivity was removed by the filter about 60 percent of it remained in the plasma.

The good news is that although there has

been some fear that filtration might fragment cells and release infectivity into plasma, that didn't seem to happen. The other good news is that there is still no evidence to suggest that there is intrinsic infectivity of either red cells or platelets. The infectivity found there appears to be attributable to contamination with plasma which suggests the possibility of technical solutions to reduce the risk more.

Peter Gantz presented recent Canadian policy actions and discussed possible future actions. I've mentioned those. Dob Scott presented the summary of the current policies and then Alan Williams addressed what it would do in reducing risk and what the cost might be if additional policies or enhancement to the current policies were adopted. Next slide please.

This is a crude reduction of some of the information that Alan presented. First, let me remind you that the deferral policies are risk reduction policies. It's not possible to eliminate all risk by deferral policies for the following reason.

If we attempted to defer any donor who had ever been in a BSE country after the beginning of 1980, we found the following projections. If we

attempted to defer anybody who had been to the United Kingdom, 23 percent of current blood donors would be deferred. If we tried to defer anybody who had been to any one of the 23 BSE countries, well 22 BSE countries, we won't even mention Canada, 36 percent of current donors would be deferred. It's simply not within the realm of the feasible.

Now let's look at what enhancing current policies might be predicted to do and these are very rough estimates based on certain assumptions. If we attempted to reduce the acceptable time, the time that a suitable donor might have spent in the U.K. during the time period mentioned from three months to one month, we would expect to reduce the risk by an additional four percent over the current 91 percent total estimated risk reduction achieved by the deferral policy and a cost in donors of about three percent which is a very large increase in the number of deferred donors.

If we deferred for transfusion in France, the amount of risk reduction is not quantifiable. But it would be very small. However the loss of donors would also be very small. Alan estimated about a loss of about 1.4 donors per 10,000 and for history of transfusion in Western Europe including France

outside the U.K., also an uncertain very small reduction in risk but at a cost of only a total of three donors lost per total of 10,000. Next slide please.

So we put the three questions to the Committee. Are the measures currently recommended by FDA to reduce the risk of transmitting CJD and vCJD by blood products still justified? Do the recent scientific data on vCJD warrant consideration by FDA of any additional potentially risk reducing measures for blood and blood products? If so, comment on the additional risk reducing measures that FDA should consider at this time? Next slide please.

The Committee voted unanimously, 14 to zero, that the current measures remain justified. However, they voted 13 to 1 that the recent new scientific data do not warrant consideration of any additional potentially risk reducing measures for blood and blood products. The one holdout felt that we really needed more information about the seven European cases whether they might have had blood exposure and clearly, that member felt uncomfortable about not deferring donors transfused in non-U.K. BSE countries. After the vote, that concern seemed to be met with some sympathy by other members of the

Committee as well, I must say, by FDA staff. Thank you very much. I don't know if there's time for questions, but if there is, I would be happy to answer any that I can.

ACTING CHAIRMAN ALLEN: Thank you for that very complete summary. I will comment with regard to Question No. 2. I think everybody on the Committee who voted no did so with the understanding that they did not believe there was sufficient data or information available at the present time to warrant consideration of specific measures, but clearly there was an expectation that the FDA would continue to monitor the situation as would be blood collection centers and transfusion medicine specialists and that as new information became available, the FDA would bring it to the Committee for consideration. Other questions or comments?

DR. ASHER: I might say in regard to that. We are committed to reevaluating the situation every six months regardless and bringing the issue to, and of course we watch it all the time, the Committee whenever new information as it did in this meeting warrant formal consideration.

DR. HOLLINGER: Dr. Asher, did you say that they are deferring persons who have had

transfusions after 1980 from the U.K.? I'm not sure I understood that. In the U.K. but not here.

DR. ASHER: No, people who have received any transfusion in the United Kingdom after 1980 to the present deferral of such people is currently recommended.

DR. HOLLINGER: In this country.

DR. ASHER: In this country.

DR. HOLLINGER: As policy.

DR. ASHER: As policy recommendation.

ACTING CHAIRMAN ALLEN: Okay. Thank you very much. We'll move on to our second committee update which is a statement on Supplemental Testing for HIV and HCV. Dr. Ruta.

DR. RUTA: Good morning, Dr. Allen, Members of the Committee. Thanks for the opportunity to update you on HIV and HCV Supplemental Testing. I'm Martin Ruta. I work in the Office of Blood and if you go to the next slide.

I wanted to update the Committee on supplemental testing and I hope it's helpful, but I wanted to step back a bit and talk about the testing schemes and this is FDA's current policy considerations on donor screening for example for HCV. So one way in which one can view the testing scheme is

for blood establishment and the requirement for testing falls with the blood establishment. It's a test donation with a license owner screening test that detects the antibodies of HCV. Then hopefully, all those donations are negative.

As the committee remembers over the past ten years, we've encouraged the development of NAT to capture window period cases. So if the donation is negative, one can view it as sequentially although in blood establishments, it occurs contemporaneously. And one goes on and runs the NAT test and that captures the window period units. So hopefully both tests are nonreactive and donation is used.

Now if one runs the HCV antibody test and the test is reactive, then one can go straight to perform the HCV supplement test. In fact, that's what occurs in the source plasma setting for applicant donors. So I wanted first to have the Committee understand that there are different practices that occur in the blood-for-transfusion setting with regard to NAT testing versus the source plasma setting. In the source plasma setting at least for the applicant donors, if the donation is reactive on the HCV test, they go straight to the supplemental test. So we can go to the next slide.

The next slide says essentially the same thing, but it's now for HIV. So as the Committee remembers, we put a rule into place that says blood establishments have to test for HIV and HCV, they have to use one or more donation as needed to ensure the blood is safe, but we've currently recommended that donations be tested for antibodies to HIV and we have a draft guidance document that's recommended that donations also be tested for NAT.

And again if one runs through this scheme, if one tests the donation using the test to detect antibodies to HIV and that's negative, then one goes on to the licensed NAT test and that's intended to capture the window period units. All right. That's what pretty much happens in the volunteer blood-for-transfusion setting. In fact, my understanding is that they are both run essentially contemporaneously.

In the source plasma setting again for at least the applicant donors and these are the first time donors or people who have not donated in six months, that the HIV antibody test is run and if it's reactive, they go straight to the supplemental test. Now as I mentioned, we've issued a draft guidance recommending the use of NAT and it's my understanding that the final guidance will be coming out very, very

soon and possibly may be posted today on our website. So I would encourage you to start looking for it.

Okay. I hope that's helpful to try and explain that there may be different testing schemes that occur within the blood collection setting. Now I want to move on to supplemental testing and this was an issue that we brought to the Committee last March. We asked for the Committee's advice on supplemental testing.

So the current requirements that are in the Reg are up here and I won't read it to you except to say that what we require is that if a donation test reactive on one of the screening of the test, that the blood establishment must go on to further test the donation with the license supplemental test if such a test has been approved.

So the reason that we put in supplemental testing requirements into the Regs is first to clarify for the donor their status whether they are really infected or not. It also places a role in donor reentry. As part of their report that the GAO wrote in 1998, they were finding that not everyone was doing supplemental testing and in fact, that there was inconsistency in notification messages and not everyone was being notified. So we put in

requirements of both, that supplemental tests be performed and that the donors be notified when they are deferred and of their test results. The next slide and the next slide.

All right. So we brought the issue of supplemental testing to the Committee last March for your consideration and we thank you for your thoughtful discussion. Actually we tried to bring it a year ago September, but we were rained out and we had the discussion last March on supplemental testing for HIV and HCV. At that point, the Committee, I think what you advised us to do is review the existing algorithms and to look at additional data.

What we've done since then is to establish a public health service working group to try and look at all the data that was collected and try and make some sense out of it. I think where we were last March was that we saw presentations from several people which showed a correlation between EIA reactive samples that were also NAT positive showing that these were truly infected individuals.

A number of the members of the Committee thought that if both the EIA and the NAT were positive that in fact the license supplemental test would not be needed. But the data that we saw last March or the

Committee saw last March primarily involved only one of the license NAT tests and in fact there are three FDA approved NAT tests and they are in order of approval, the National Genetics Institute UltraQual HIV I and HCV Test, the Procleix HIV I/HCV Multiplex test and the Roche COBAS HIV I and HCV test.

So we established a PHS working group. If I can go to the next slide. We tried to address a number of scientific questions and these are limited to the blood bank setting. We started off with what we were hoping would be the simple questions and that is if donation is reactive/positive on a license HCV NAT on a single donation and the same donation is also HCV antibody reactive, can those results be used to confirm infection in lieu of the HCV supplemental test? The answer that we came up with was yes, you could.

We asked a similar question for the HIV testing and the reactive/positive results of a license HIV NAT performed on a single donation that is also HIV antibody reactive. We used to confirm infection in lieu of the HIV supplemental test and again the answer we came up with was yes, it could. So let me explain here for, I said, reactive or positive results. In the case of the multiplex test, we

actually mean that it's discriminatory reactive. It's reactive with a specific primary for either HIV I or HCV. Okay. If I can move onto the next slide.

I've told you the answer already but where the Committee came out and where the working group is that if the donation is reactive on the HCV EIA screening test to detect antibodies of HCV and the donation is reactive or positive on an individual sample using a license HCV NAT meaning discriminatory reactive for the multiplex test, then as a scientific matter, the license HCV supplemental test would not be needed to confirm infection. This is a scientific statement and as a regulatory requirement, the supplemental test is still required and I'll get to that at the end.

So moving on to the next slide, we come to this, and I've given you the answer for this already for HIV. For HIV supplemental testing where both the EIA is repeatedly reactive and the NAT is positive, we've said that as a scientific matter, the license HIV supplemental test would not be needed to confirm infection. All right.

So now we deal with the more complicated issues in the next slides and that is what happens when the tests don't agree. I think this is sort of

where the Committee was left to consider some of the data that was presented and wasn't quite so sure. Where we ended up that if a donation is reactive on a license HCV EIA donor screening test to detect antibodies for HCV and the donation is nonreactive or negative using an appropriate license HCV NAT, negative or nondiscriminated on an individual sample, then as a regulatory requirement, the license HCV supplemental test would still be needed to provide information about the donor's infection status. So these are the ones that are EIA reactive NAT negative. So the RIBA is still needed.

If we go onto the similar consideration for HIV in the next slide, again if the donation is reactive on the license HIV donor screening test to detect antibodies to HIV and the donation is not reactive or negative on the appropriate license HIV NAT or not discriminated on the individual sample, then as a regulatory requirement the license HIV supplemental test would still be needed to provide information about the infection status of the donor.

Let me correct what I said before. Here's where there was a bit of a debate about the science involving alternative schemes to try and resolve HIV infections. So we recognize that there's still a

scientific debate involving the use of alternative tests to resolve HIV status.

And if I could go to the next slide. So what have we done? We actually have received a variance request from a blood establishment and we've issued a variance under 641.20 to allow a blood standard to not perform the HCV supplemental test which is a required test under 610.40(e) our testing requirements when the donation was reactive on a license HCV EIA for antibodies and also was positive on the license HCV NAT on an individual donation. If I can go on to the next slide.

There are possible other courses that we could use to address this issue. One would be we could consider whether to relabel the HIV and HCV NAT test, the supplement test, when the NAT is positive. That would require manufacturers actually to come in and seek such changes and we would entertain those requests. In addition, we may need to relook at the regulations requiring supplemental testing and consider changes to those in the future.

Finally, well, almost finally, other issues. Okay. So now we deal with the more complicated issues that I think the Committee was pondering last March. If you remember there were a

number of data sets presented and I think what the Committee was struggling with is that there were discordant results on the same sample. So we had donations that were EIA reactive NAT negative or positive on the Western blot but then had been tested on other EIAs and were discordant on some of the EIAs. The Committee was sort of pondering what does this mean and how do we sort this out.

Where I think a step further into the datasets and at this point, we have a lot of questions, just to give you an idea for the type of things that we are looking is some of the discordants actually had very high signal to the cutoffs and were negative on one EIA and positive on another and we had some questions about those. There's been a limited amount of retesting and there may be some testing issues with those particular samples.

There were additional samples that I was hoping that our laboratories could obtain and test for us that have not been retested yet. We run into a phenomenon of the Federal Government where we came to the end of the fiscal year and basically they told me we didn't have any money. So I'm hoping now with the continuing resolution that our laboratories will be able to do some of these studies that I was hoping

that they could do.

I think the, I see my time is signaling. So I'll try and wrap up quickly. There are a number of other questions that we're facing with the datasets that were presented and that is how do you know, a number of the presenters were suggesting that the blots were actually false/positive blots and that some were actually real infections.

One of the first questions that we asked was how do you know which ones are real and which ones are not real. We've asked for additional data to sort out which ones are real and which ones are not real. We're waiting for some of those datasets to arrive.

Some of the other issues that we are struggling with are minor things like there were band patterns that were presented which included molecular weights that are not described in any of the current inserts so I presume were errors in transcription. We're dealing with issues that the datasets again involved only one of the NAT tests and only involved the whole blood sector.

We actually didn't see any data from the source plasma sector and whether we would need these additional datasets. So we're wading deeper into the data now and in an interactive dialogue with the

presenters and trying to figure out what data is needed. Finally, I'd like to thank the members of the PHS working group who are up here on the slide. So I'll stop and see if there are any questions from the Committee.

ACTING CHAIRMAN ALLEN: Thank you, Dr. Any comments or questions? Yes, Dr. Lew.

DR. LEW: I just wanted to know what percentage of patients who are donors have actually been EIA Western blot positive but NAT negative.

DR. RUTA: Right. Well, this would come from the datasets that were presented and I think in those cases that datasets that we saw ran around five percent of the donors were Blot positive, EIA Blot reactive positive but NAT negative. Now some of those were said to be real infections and other were asserted to be not real infections. So we're trying to sort through those.

ACTING CHAIRMAN ALLEN: Other comments or questions? This is obviously a very important area and we look forward to further discussion about that in learning how the FDA intends to resolve it. We will actually deviate a little bit from our published agenda at this time and move to an open hearing if you will and allow Dr. Kleinman to make a combined

statement on HIV and HCV supplemental testing. This is a combined statement from the AABB, ABC and ARC. Yes, if you would like to come up here, that would be fine.

Now I need to read a statement first because this is an open public hearing. So bear with me. Open Public Hearing Announcement for General Matters Meetings. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency, at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

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

Likewise, FDA encourages you at the beginning of your statement to advise the Committee if

you do not have any such financial relationships. If you chose to not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. Dr. Kleinman.

DR. KLEINMAN: Good morning. I'm Dr. Steven Kleinman, Chair of the AABB Transfusion Transmitted Disease Committee. With regard to conflict of interest, I do have and have had some consulting arrangements with companies that manufacture NAT assays.

I'm reading this statement today. It's a joint statement endorsed by AABB, American Bloods Centers and American Red Cross. Our statement today is similar to that presented to the Committee in March 2004 when supplemental testing for HIV and HCV was last discussed. The purpose of today's statement is to emphasize the importance of this issue and the urgency to make rapid progress especially with regard to HIV.

AABB, ABC and ARC strongly endorse the revision of supplemental testing algorithms for donors testing EIA, Repeat Reactive for HIV and HCV antibody as previously presented to the Committee during the March 18 meeting. These algorithms were subsequently summarized in a letter from AABB to Dr. Epstein on

August 10 of this year.

We acknowledge the FDA for moving forward with the integration of nucleic acid tests into supplemental testing algorithms. The extensive amount of data presented at the March BPAC meeting clearly established the scientific validity of using reactive NAT to determine the existence of HIV I or HCV infection in EIA repeat reactive donors. In such circumstances, HIV I Western Blot and HCV RIBA add no useful information to the evaluation of the donor's status.

So this is good that we heard today that FDA and the PHS Committee are scientifically in support of this. However the inclusion of NAT in the HIV supplemental testing algorithm will not prevent the classification of many donors as HIV Western Blot indeterminant since only three percent of HIV I/II repeat reactive donor samples are positive leaving 97 percent of such specimens to be tested by Western Blot. In cases with non-reactive HIV I NAT and alternate HIV I/II negative alternative HIV I/II EIA results, the data indicate that the Western Blot has no usefulness.

It's not surprising that in alternate HIV I/II EIA is superior to a Western Blot for

confirmation of HIV I infection. This is a direct consequence of the continued improvements in the sensitivity of HIV I/II EIAs.

In contrast, no similar improvements have occurred since the first use in the licensure of HIV Western Blot. We now and have for some time been in the paradoxical situation in which the Western Blot originally licensed as the HIV I supplemental assay is less sensitive than is screening EIAs and is certainly the least specific test used in the blood donor setting.

While the scientific validity of using NAT or an alternate EIA in supplementing testing algorithms is a necessary prerequisite for making a change, there is a much more compelling reasons for such a revision. Indeterminant test results create confusion and anxiety for the donor. This is well documented by REV's investigators who surveyed donors about their perception of and reaction to the notification process.

Responses were received from 203 donors with indeterminant results for HIV antibody or P-24 antigen, HCV and HTLV. These data published in "Transfusion" and presented at the March BPAC indicate that the vast majority of such donors were both upset

and confused when initially notified of their test results and remained upset and confused six to 12 months later. This is not surprising when donor have been told based on their indeterminant Western Blot results that there is some possibility that they are infected with HIV I.

Unfortunately, such notifications are not confined to only a handful of donors. According to American Red Cross data, approximately half of all HIV EIA repeat reactive donors have an indeterminant Western Blot result. When the ARC data are projected nationally, we estimate that over 5,000 donors receive this message annually in the U.S.

This translates to anxious donors contacting blood centers each day confused and frustrated about their HIV indeterminant result or occasionally and even worse, their false positive HIV Western Blot results. This situation has not changed since 1987 so we've been living with this now for 17 years.

Instructions for carrying out the HIV I/II EIA screening assay state, it is recommended that repeatedly reactive specimens be investigated by an additional more specific or supplemental test. Since the majority of donors with indeterminant Blot results

are not infected with HIV I, it is apparent that the Western Blot assay is not achieving the enhanced specificity expected of a supplemental assay.

Until recently, this situation was a necessary but unfortunate outcome of the notification process given that there were no alternate means of assessing the donor's infection status. However, such disservice to the donor community cannot be justified when we have the tools available to do better. Testing technology has advanced to the point where donors would be more accurately apprised of the meaning of their test results if FDA were to permit blood centers to use the AABB proposed testing algorithms.

The Committee has agreed that revised supplemental testing algorithms is the correct course of action that this Committee, the BPAC, based on scientific and ethical considerations. However there still appear to be hurtles to cross. As Dr. Ruta told us, 21 CFR 610.40(e) states that you must further test each donation including autologous donations found to be reactive by a screening test whenever a supplemental, that is an additional more specific test, has been approved for such use by FDA.

Now NAT assays or licensed HIV I/II EIAs

do not currently carry these supplemental testing claims. However these assays have undergone rigorous review by FDA for donor screening claims and as such they meet all CGMP requirements including those for clinical and analytical sensitivity, specificity and reproducibility.

Furthermore, over five years of data establish the usefulness of NAT to confirm HIV I and HCV infection status supplemented by HCV RIBA or HIV I/II alternate EIA in circumstances in which many pool (PH) NAT is nonreactive. The use of an alternate HIV I/II EIA coupled with IV NAT, individual donation NAT, as included in the AABB proposed algorithm will serve to reduce substantially the number of HIV I Western Blots that will need to be performed.

Considering these facts, we urge BPAC to recommend to FDA that it find a way to allow both NAT and the HIV I/II alternative EIA approach to be a major approach of HIV and HCV supplemental testing algorithms without requiring new clinical trials to establish this claim. To this end, we also encourage the manufacturers of NAT and the HIV EIAs to work with blood centers to submit the required supplemental claim data to FDA for expedited review.

Lastly, and I think very importantly, use

of the proposed supplemental testing algorithms has no impact on blood safety since all EIA repeat reactive units are discarded and the donors are deferred. Furthermore, these algorithms, the use of these other supplemental tests like an alternate EIA, is not being proposed for the purpose of donor reentry.

So to restate this is a tool by which to give donors better notification methods, not a tool that at all affects whether the unit will be transfused or whether the donor will be eligible in the future. Therefore, supplemental testing algorithms should be adopted based on their ability to provide a timely and accurate result to a blood donor who is taking the time to make a generous gift. The AABB proposed algorithm is well suited for the purpose of accurately informing a donor of test results. Thank you.

ACTING CHAIRMAN ALLEN: Thank you, Dr. Kleinman. Any questions or comments for Dr. Kleinman? Thank you. At this point in the meeting, we will go back to our opening since Dr. Epstein is here. We will go ahead and proceed with the Topic 1 which is FDA's current thinking on reentry of donors previously deferred for anti-HBc reactivity. We have a series of four presentations in this segment. The first

introduction and background by Dr. Kaplan. I'll be pleased when wireless technology simplifies the transfer of computers.

DR. KAPLAN: Good morning. I'm Geraldo Kaplan. I will introduce for you the reentry for donors that were deferred for repeat reactivity with anti-core tests results. So this is a current thinking session and the FDA would like to present to the Committee a proposed algorithm that will allow reentry of donors deferred for testing repeat reactive for antibodies to hepatitis B surface antigen on more than one occasion.

This guidance dated September 10, 1991 for the screens of anti-HBC it says that donations for transfusion should be tested for HBsAG and anti-HBc. Only reactive units should be transfused. The donors should be indefinitely deferred when they test repeat reactive more than once and that donor reentry algorithms were not recommended at that time because there was no supplemental test, basically a more additional more specific test for anti-HBc.

The consequences of this anti-HBc screening were that although anti-HBc donor screening contributed to blood safety, many donors were indefinitely deferred because of potentially false

positives anti-HBc results. In the BPAC meeting in December 1998, FDA and AABB presented to BPAC similar reentry algorithms based on negative test results for hepatitis B surface antigen, anti-HBc and anti-HBsAG.

The Committee did not recommend reentry because the American Red Cross data showed that some HBsAG and anti-core negative samples were HBV reactive using an experimental NAT. As you stressed that in some tests the anti-HBV were also positive so some samples where one was positive with one test and negative with another one.

We have had recent developments basically that hepatitis B in NATs have been developed for screen donations in meaningful format. They can be used to test individual donations. It does enhance its sensitivity. The FDA is considering testing algorithms to permit reentry of donors that will include use of this sensitive HBV NAT and I will talk about that proposed algorithm in a few minutes.

Some of the considerations is that will permit reentry only on the premises that (1) historical test for anti-HBc were false positives and (2) that there is no evidence for past or present hepatitis B virus infection. Also reentry base on testing of hepatitis B surface antigen, anti-core and

hepatitis V DNA by the NAT that antibodies to HBsAG is not part of this reentry or algorithm because extensive hepatitis B vaccination programs have been in place for a number of years and many individuals are antibody positive so this is not a good marker of hepatitis B infection at this point.

So what's our current thinking? A donor that has been indefinitely deferred because of having tested repeated reactive for anti-HBc on more than one occasion may be reentered if after a meeting of eight weeks subsequent to the last repeated reactive anti-hepatitis B core test a new sample is collected from the donor and this sample tests negative for surface antigen, anti-HBc and hepatitis B NAT and the sensitivity that we're looking for is 95 percent detection at less than 10 copies per mil. However, we are at this point flexible on that limit and this test should be FDA license assays.

Also that whenever a donor presents at a blood center to the NAT subsequent to the negative test for surface and anti-core and HBV NAT, all donors with that criteria for donors of whole blood and components are fulfilled. So basically that's what I would like to present to you. The data of the full evaluated algorithm is being collected at the present

time and basically the part missing is using a more specific test for anti-core. So we will hear a presentation by Dr. Susan Stramer regarding her data on NAT testing of repeat reactive samples. At this point, I would like to introduce Dr. Blaine Hollinger that will give us an introduction on serology.

ACTING CHAIRMAN ALLEN: Can we take just a second first? Are there any questions first of all for Dr. Kaplan's setting of the stage? I've have just one quick question with regard to the sensitivity of the HBV NAT. You talked about a sensitivity of 95 percent detection at 10 or fewer copies per MIL. What is the range there that you actually find in the FDA license assays?

DR. KAPLAN: Well, there is no license assay. The FDA last week presented a set of possible license in the near future of HBV NAT. That is a meaningful assay so the sensitivity of that meaningful assay that it's lower than the ID NAT in donation. Unfortunately, I think that Rush (PH) had given a presentation, the last presentation of the session. I haven't seen him in the room. They are here. Good. So they will probably talk about the sensitivity of their assay that would meet this 10 copies requirement and I understand that other assays could reach that

limit though we are flexible at this point on that requirement. So restating what I'm saying is that the future license test are meaningful and this is probably pushing a little bit the envelope because it will be done on ID NATs single units.

ACTING CHAIRMAN ALLEN: All right. Thank you. Dr. Hollinger.

DR. HOLLINGER: Thank you, Dr. Allen. I'm going to try to give again a brief overview of serology to those of you who may not be quite so familiar with the hepatitis B virus. I think any time that you start with serology you need to understand something about the mechanisms briefly of viral multiplication.

With any viral infection usually initially specific cells are targeted for infection and of course where hepatitis B virus this is the hepatacytes. The genetic material then from that virus is introduced in some fashion into the cell. Following this, genes are expressed and viral genomes are replicated and following this replication there are both non structural proteins which are important for the viral replication as well as structural proteins which are important for the assembly and release of virions. In most cases following this but

not always cells are destroyed and disease develops.

This shows these particles that are found in hepatitis B virus infections. It's really interesting because initially we were all expecting to find really virions present and in this virus, you found a very large number of these non-infectious particles. Indeed the plasma derived vaccine initially was made from this small particle here. These long tubular forms, the tubulars you can see coming off of the surface of the virion itself is the surface antigen is composed of these small particles here.

There is no infectious nucleic acid in these particles. So you have surface antigen here and on the surface of the virion itself, there is probably 10,000 or more non-infectious particles per each infectious virion that's present. Then of course inside this virion is a nucleocapsid that protects the nucleic acid which is inside of this particle. Next slide please.

The nucleic acid for hepatitis B virus has four open reading frames. Two of them are important for the discussion here today and that is the open reading frame which is important for the surface antigen and of course it has its own antibody, the

anti-HBs and then there is the open reading frame that produces the core antigen important for the nucleocapsid. Part of this core antigen also is important for the production of the HBe antigen. The e antigen is not part of the structural protein of the hepatitis B virion but does circulate free in the circulation indicative of an active replication of virus. Next slide please.

This just again shows the life cycle of the hepatavirus. It enters the cell. The coating is taken off. The nucleocapsid gets into the nucleus from which there is transcription of the genome with translation. It is then packaged into the nucleocapsid where there is synthesis, minus strand and plus strand synthesis. It's then budded. It goes through a budding phase in which the envelope is found in the virions which is then exported out the cell. Next slide please.

It is interesting. If you look in this cell, this is a freeze fracture EM if you will of a cell and what's very interesting in these cells is that there are nucleur pores. We wondered how these nucleocapsids could get inside the nucleus as well as being present in the cytoplasm. So this slide shows these nuclear pores and the next slide please.

This shows an infected cell with hepatitis B virus in which the nucleus is loaded with these small nucleocapsid some of which or most of which contain the virion. There are also nucleocapsid here in the cytoplasm. Indeed in the very early phases of infection, nucleocapsid is probably excreted free into the blood stream. In fact even as long ago as 1975, we reported the presence of free nucleocapsid in the blood of patients in the early phases of their infection which was found at that time with DNA polymerase but it preceded the development anti-core or anti-HBc. Next slide please.

Now what about the course of HBV infection in general. Next slide.

Before you understand anything about the course of infection, you have to have some grasp of the sensitivity of the assays which are available today. This slide goes from micrograms down to attograms here. Picograms, fentograms and attograms and so on getting down the HBV genome. The hepatitis B virus has one picogram of the HBV virus which is equivalent to about 280,000 genomes in there. So that's about at that level.

The hepatitis B surface antigen test which are currently available, I mean the unlicensed test.

Some of the unlicensed test can get teched down one tenth of a nanogram or less in this range here which is approximately 100 picograms. You also then see that as you get into radioautography, hybridization assays maybe that could detect in this level here, some of the very first assays might detect only 750,000 genomic equivalents and then as the tests were developed and you got into PCR and then into nested PCR and into some of the amplification assays, you began to move down toward this range here where you're almost testing or evaluating one HBV genome circulating per ML of blood.

So all of these tests are important because it tells us something about some of the studies that were done previously when, look at the next slide and you can see this on the next slide. Let me go on with this first. HBV DNA in the blood is detected about two to five weeks after infection and up to 40 days before the hepatitis B surface antigen is detected with a mean of only six to 15 days. It rises slowly. It's distinct from hepatitis C virus infections and it's at a relatively low level perhaps maybe only 10,000 genomes per ML or 100,000 or less during the seronegative period. Next slide.

HBsAG appears one to three week before the

ALT becomes abnormal or three to five weeks before the onset of symptoms or jaundice. It reaches the peak during the acute stage of the disease and then it declines to undetectable levels within four to six months in most of the individuals who resolve their infection as is true for probably 97 to 99 percent of immunocompetent individuals, adults. Next slide.

This slide I think points out again the relationship between HBsAG and HBV detection as we get more sensitive. The earlier tests maybe could only have a limit of detection of about 1,000. When you look at HBV DNA and those only about 66 percent of them were positive for HBV DNA.

As the tests became more and more sensitive and we are now down to 20 or 10 or 1.3 IUS per ML of detection, you can see that virtually all or at least most of the HBsAG positive material contains HBV DNA. This also just throws in here at these levels here some of the positivity in samples that are anti-HBc positive only, about 13 percent with this particular report and nine percent here. Next slide.

The third product is IgM anti-HBc. IgM of course is one of those early acute phase products which occurred. It's indicative of on-going viral replication when present. It appears acutely at the

onset of an ALT abnormality. It's primarily in the acute phase a 19S component. It's present but undetectable in some chronic infections.

Some people would say most chronic infections at a level that you usually don't detect it because a current IgM assay starts at an evolution of one to 1,000. This was initially set up to avoid a prozone (PH) which occurs at one to 100 levels or higher.

It is a 7S IgM fraction. That's kind of interesting because some of the new reductant assays that are available that use reductants like cysteine e or diathiathriatol (PH) usually break down the 19S component to a 7S component and often are more sensitive because of that when you add specific antibody present. So you don't lose the sensitivity of the assay in most cases. The IgM anti-HBc may reappear during reactivation of HBV. Next slide.

Now the total anti-HBc test and we say total just like we do for the total anti-HAV test is because it can detect both IgM and IgG. It is not just an IgG assay. It is detected in past or present HBV infections. It does not result from the hepatitis B vaccination which uses only HBsAG and therefore the antibody response is only anti-HBs. Next slide.

And finally you have anti-HBs which comes later. It is the neutralizing antibody which occurs during recovery and after vaccination. It may become undetectable in up to 20 percent of patients after several years of follow-up. The next slides shows this.

If you can see here, here's an acute infection here and after many years, what happens is the anti-HBs is not a very strong immunogen as compared to the anti-HBc and so the antibody levels that circulate in the blood stream are much lower. So over time, the anti-HBs may disappear. It's very unusual for the anti-core antibody to disappear. So out here many years later, all you'll have is anti-HBc only.

If you take these individuals and vaccinate them or give them the regular vaccine within two to four weeks they will generate an anamnestic response which is one way you can try to determine whether or not this is anti-HBc only from a remote infection as distinct from something else. Next slide.

This slide then looks at the serology of the disease and again as we pointed out what happens is HBV DNA occurring early followed by the HBsAG and

the e antigen present here in the bloodstream. IgM anti-HBc occurring early, switching over, not switching over but really switching very early with some IgG here as well and then both circulating. The IgM disappearing. The IgG continuing.

So what you have from this kind of slide here is you show that if you want to evaluate the relative infectivity of the blood, then HBV DNA and HBeAG is the most important thing to look at. e Antigen positive specimen in most cases is indicative of a very active infection with lots of virus in the bloodstream. There are exceptions to everything we talk about here but in general that's a very good rule.

The second rule is that the presence of IgM anti-HBc helps you differentiate in most cases acute from chronic infection. And a third rule is that the presence of anti-HBs and anti-HBc is indicative of immunity. Next slide.

This then shows the progression to chronic hepatitis B. Of course in very young infants born to mothers who are e Antigen positive perhaps 90 percent of these infants will become chronically infected. But for the immunocompetent adult, it's probably one to three percent that will become chronically

infected. We used to think it was 10 percent, but we know now that many of those patients had reactivation of chronic and not really acute hepatitis B which is why that initial level of 10 percent was felt to be the resolution of disease.

So in this case what happens is the patient becomes positive. Their HBs antigen remains elevated for more than six months. That's an arbitrary level to establish chronicity from nonchronicity. As you get more sensitive tests, of course I'm sure those arbitrary levels might have to change a little bit, but basically these patients remain HBsAG positive with a total anti-core.

There is no antibody that's usually developed that you can detect in most cases. They are e antigen initially and as years and years go by, about five to 15 percent a year will go from HBeAG positive to anti-HBe positive. Usually it occurs with reactivation of their disease. Enzymes go up. They may even get jaundice and look like acute hepatitis B.

This limited detection is very important because some patients can circulate virus at very low levels below the detection limit of your assay and therefore they will be negative but there may be anti-core present only and that may indicative of that

disease. Next slide please.

Now this sort of summarizes a couple of things which I've said and it goes through the factors that we just talked about. These are HBV DNA column, HBsAG, anti-HBc and anti-HBs. The first new HBC DNA positive is usually in the presero-conversion window period.

Next, if they develop HBsAG but are still negative for anti-core and anti-HBs this is usually in the early acute infection. Anti-core is then developed which is then indicative of an HBV infection either acute or chronic. You can't tell at this stage unless you do IgM anti-core.

As I mentioned, a few patients will have IgM anti-core who have chronic disease. The difference is is that IgM anti-core is at very low level, usually below three times the cutoff level as compared with an active acute infection which is very high. So that's a good way of determining whether this is an acute reactivation of a chronic disease versus acute disease.

Then you have patients who are anti-HBc and anti-HBs positive but have no DNA or surface antigen. This is usually indicative of a previous infection with immunity. Next slide.

The thing we're going to talk about a lot today has to do with this group here which may or may not have HBV DNA in the blood. They are negative for surface antigen but they are positive for anti-core. The total anti-core, I'm talking about here and they are negative for anti-HBs. This could indicate either a low level carrier as we talked about where the antigen cannot be detected.

It could be an early convalescent period in which case the IgM anti-HBc will be positive and these patients will also be anti-HBe or HBeAG positive as well in that window period. It could be HBV infection in the remote pass as I discussed a minute ago or it could be a false positive or nonspecific reaction. A fifth one would be passive transfer of anti-HBc as say from a mother to her infant or through some blood products.

Finally, the other ones. This is a patient for all of these markers here but positive for anti-HBs. This is the kind of response you would expect after receiving the vaccine. Then of course if they are all negative, it usually excludes HBV infection. Next slide.

I want to just dwell just a little bit on the anti-core positive only group, the isolated group

or the solitary anti-HBc group. This just looks at the prevalence of isolated anti-HBc of blood donors and HBV DNA in those samples. It's a large group of patients, about eight studies here with a large group of patients and you can see that the anti-HBc only population, that's without anti-HBs, but anti-HBc only, no HBsAG, no anti-HBs, that it goes from a 0.07 percent up to 4.8 percent depending on the region of the world with sort of a median of somewhere around 0.3 percent.

The HBV DNA levels in these studies again you have to remember that there are different degrees of sensitivity when these assays were done, but they ranged here from zero up to 3.9 percent positive in those particular individuals. Next slide.

This slide shows the HBV DNA detection in anti-core positive only blood donor samples. Depending on the prevalence of chronic HBV infection in a population in this group the HBV DNA detection was 3.7 percent. In a population where there was a lot of virus around in that endemically, it was up to 24 percent in this study. Next slide.

Now finally the last thing I want to talk about is just a little bit about HBV transmission from HBsAG negative donors. Next slide.

I'll start just briefly with a study that we did many years ago and again you have to understand that the sensitivities of the assays change and that's why I want to bring up this study because it points out the difficulties with looking back 10, 15, 20 years ago or even looking at assays that were done 10 years or so. In that study, we found HBV infection occurring in about one percent of the recipients of blood transfusions that were anti-core positive, but HBsAG negative and the untransfused control was less than ten percent.

There were five recipients who were co-infected with HCV in this study. I'm not talking about those. There were ten that had 12 implicated donors with HBV alone. Next slide.

Six of these donors, now this was done as I told, these were all HBsAG negative by the initial test that we did, but with a more sensitive test about ten years ago, three of them were actually found to have HBsAG in their bloodstream. It may be possible with even the more sensitive assays today that some of the other assays, some of the other donors, may also have HBsAG if you looked at them with the newer test. But there were six individuals here that were positive for anti-core, negative for HBsAG and HBV DNA. The

same thing I said about HBsAG can be said about HBV DNA. Next slide.

In this particular study of the individuals that were anti-core positive only that had no anti-HBs, 17 percent of those donors were associated with a hepatitis B case. Of the individuals that were anti-HBc positive that had anti-HBs in their blood up to 9.9 MIUs per MIL or International Units per liter, ten percent were associated with the case and most importantly, none of the donors that were anti-core positive only that had a high level of anti-HBs were associated with the case.

I must say that going through the literature I have yet to find a case of hepatitis B that has been transmitted from an individual who had anti-HBs and anti-HBc with a level that was at least above 10 or certainly above 100 regardless of their HBV DNA status. Next slide please.

So in looking at the risk of hepatitis B following receipt of anti-core positive products from blood or organ donors, 17 percent in our study here showed this. Allain showed three at ten percent.

Among organ donors, it's much higher. These are now organs that were given, not

transfusions, but organs that were given from patients who were anti-core positive and they may have anti-HBs and you can see a very percentage of those showed the development of hepatitis B. Immunosuppressed individuals. Next slide and the last slide.

This also shows anti-HBc transmission from pregnant females to their infants. There were 66 mothers with anti-HBc reactivity only. Three of the infants had high ALT levels. Two had HBsAG and one HBV DNA without HBsAG. The HBV DNA was found in the leukocytes of two carrier mothers and in the cord blood of leukocyte samples, the infants became carriers with elevated ALT levels.

So I hope that this gives you some idea now as we're going to start talking about these issues about anti-core gives you a background of the serology of this disease. Thank you very much.

ACTING CHAIRMAN ALLEN: Thank you. A quick question. You showed data about the 12 donors that were implicated in transmission and then tested with later or more recent assays. I assume the testing was done on old stored samples of serum.

DR. HOLLINGER: It was done on stored samples, stored minus 70.

ACTING CHAIRMAN ALLEN: Thank you.

Questions for Dr. Hollinger. Yes, Jay.

DR. EPSTEIN: Blaine, can you comment on the sensitivity of the DNA assays that were used in these retests?

DR. HOLLINGER: On the retests?

DR. EPSTEIN: Yes.

DR. HOLLINGER: They were certainly more than, I would say probably in most cases more than 100 in there, but I don't know specifically. These were done in 1993 I believe. So it wasn't the assays done with PCR. Well, there was PCR but it wasn't done with the more sensitive assays that we have today. I can't tell you exactly, Jay. I don't know.

ACTING CHAIRMAN ALLEN: Any other questions or comments? Yes.

DR. GOLDSMITH: Has the sensitivity of the anti-core changed over time, the tests that are being used?

DR. HOLLINGER: The tests that are currently being used, the licensed tests, probably have not had a great deal of change in sensitivity. I mean if you go back 30 years or 20 years, yes, but the more recent ones not very much.

ACTING CHAIRMAN ALLEN: Did it change as the antigen in the test, wasn't it initially derived

from an infected chimp or nonhuman primate lever and then became the recombinant test? I assume that the sensitivity probably changed with that. Okay. Other questions or comments? Yes.

DR. HARVATH: I was wondering in the last slide you showed where the transmission from mother to newborn, do you know whether in those studies those were from Asian countries or do you know the ethnicity of that? And would we have a different concern in a population, let's say, an Asian country where there would be higher incidence overall of HBV infection?

DR. HOLLINGER: Liana, I can't remember if those were from Asian populations or not. I have to go back and look it up again. Sorry.

ACTING CHAIRMAN ALLEN: All right. Any other questions? Our next speaker is Dr. Susan Stramer from the American Red Cross, studies of deferred donors.

DR. STRAMER: Thank you very much. For those of you who have a handout, I've updated my slides so please bear with me. But the Committee should have the new and improved version. Hopefully, it's improved. It's certainly new. Can we go to the next slide?

This is what I hope to cover today. The

current situation with anti-core testing, to show you reactive rates and the efficacy of the 2X deferral policy that Dr. Kaplan outlined, the history of the reentry algorithm development, what happened at prior BPACs which was already highlighted and then what successes we've had as a AABB task force is looked at the issue of anti-core reentry.

I'll review data of a pre-IND pilot study that we did with NGI, the current status of an IND that we have for testing anti-core repeat reactive donors for DNA which is also with NGI. Preliminary data was presented by Dr. Richard Smith at the June BPAC and then I will conclude. Next slide please.

This is during my life with the Red Cross the reactive rates of anti-core. So that's what the beginning of the X axis represents. But what you see of the initial reactive rates and the repeat reactive rates are both a linear decrease over time. So we are calling out anti-core repeat reactive donors as we lose true positives and false positives. This was 9/11 but also you see that the pattern of IR and RR rates parallel one another indicating that it's probably related to a characteristic of the test. Our mean repeat reactive rate is 0.44 percent and it's over the last fiscal year. Next please.

We know that no confirmatory test exists for anti-core. Neither does a standardized confirmatory strategy and also there's high non-specificity of tests currently in use. The historical and present repeat reactive rates I showed you ours at 0.44 percent have ranged from about 0.4 to 1.6 percent.

The estimated majority of these are false positives and from some email exchanges that we've had over the last couple of days with some blood centers, I've put together the low and high reported for blood centers of false positivity based on in-house algorithms such as anti-HBs, repeat anti-core with a second ELISA, etc. So we have this range of false positivity. It's obviously dependent on the specificity of the test used.

The policy for anti-core repeat reactivity is that if you're core reactive for the first time you may donate again. But there may be a negative impact of a repeat reactive notification on a donor returning to donate. They may not understand what we're trying to tell them. But if you're anti-core repeat reactive twice, you're deferred.

Now in trying to determine how many deferred donors we have who lack other deferrals, that

is their anti-core repeat reactive only and otherwise would be suitable for donation, the Red Cross has put together data since we have been tracking this at greater than 200,000 donors over this time period. However, the number is probably considerably higher because we and most blood centers implemented core screening in 1987 and then this doesn't include 2004. So perhaps the number nationwide if we represent about half may be close to one million donors. Next please.

What is the success of having a 2X anti-core deferral option? That may tell us a little bit about what the likelihood of donors who will come back if we did have a reentry algorithm. These data will be presented by Chang Fang and co-workers at this year's AABB meeting, but I will highlight the findings.

I'm going to present data for 3.9 million donors representing 6.5 million donations from the year 2000. They were the anti-core repeat reactive donation and continued donation history was examined from 2000, that's the index year, plus three additional years to look at their return history. We excluded autologous and donors with other deferrals.

The ortho anti-core LIs (PH) was used for the entire period of time and for this period of time,

I showed you why repeat reactive rates have been decreasing, but for this period of time, our repeat reactive rate was 0.64 percent and for control population those were anti-core nonreactive. We selected first time and repeat donors at 500 selected at random per month for the one year period of time. So we had about 6,000 for each group. Next please.

The total number of first time donors, 36 percent of the 3.9 million was 1.4 million. 1.4 percent of the first time donors tested core repeat reactive. Looking now over the next three years, 81.5 percent never came back.

In comparison to first time donors where our control was 54 percent came back. Of those who did return, that is the remainder which is about 20 percent, 88 percent were core repeat reactive at their donation. Of the remaining 12 percent who remained eligible which is 428 total donors, 14 percent became anti-core repeat reactive in the next three years. From this 14 percent, 98 had subsequent anti-core nonreactive donations from 60 donors ranging from one to seven donations per donor. The remaining 86 percent had 809 subsequent anti-core nonreactive donations and this was from 368 donors with a range of one to 13 donations per donors.

So the overall yield for first time donors who were core reactive for the first time was 0.016 donation per donor per year. I don't know if that equals to your pinky or your big toe but it's certainly not a lot of success. Relative to controls, we have 0.74 donations per donor per year from the control group. Next please.

Now looking at repeat donors, 2.5 million or 64 percent of the total, 0.24 percent were repeat donors who tested anti-core repeat reactive. Similarly to the first time donors, 80 percent did not return in three years versus 26 percent of the controls. Of those who did return, 38 percent were anti-core repeat reactive for the second time on the subsequent donation.

Of the remaining 62 percent who remained eligible, that's 752 donors, 12.5 percent were anti-core repeat reactive in the next three years. From 12.5 percent, we had 224 subsequent anti-core repeat reactive donations from 94 donors with this range, one to 23 donations per donor and for the remaining 87 percent who were not deferred in the next three years, we had 3,000 subsequent anti-core nonreactive donations from 658 donors with a range of one to 57 donations per donor. The overall yield was 0.18

donation per donor per year which relative to the controls is lower. Controls was 1.36 donations per donor per year. Next please.

You can skip this slide and skip the next slide. These were provided to the Committee to let you see how the data were derived. Next please.

So of the total 3.9 million donors in 2000, the donor return rate is low. Three hundred sixty-eight of 1952 anti-core repeat reactive donors who were first time donors, their return rate was 1.9 percent. Six hundred and fifty-eight of 549 (SIC) repeat donors successfully donated for donation over the next three years or 11 percent.

Of those who did return, high rates of 2X anti-core reactivity that was 88 percent of first time, 38 percent in repeat. The total successful donation yield per year is low and these were the numbers that I quoted, 0.16 for first time, 0.18 for repeat and 0.74 for first time controls versus 1.36 for the repeat controls or 46 and 8 times higher for the control group. That is their yield of successful donations. Next please.

So the 2X deferral policy is of limited yield. The impact is greater on repeat donors who we lose 80 percent for core reactivity on the first time

donation versus 26 percent who will come back. The anti-core reentry algorithms are projected to have higher yields if a different test is introduced. That is the blood system converts to a different method. We have two hurdles here. One is that the donors don't return and secondly, the donors continue to be repeat reactive when the same tests are used. Next please.

So where do we stand? At the December '98 BPAC, this was reviewed by Dr. Kaplan, but it was our data that caused some concern. We were involved in the PRISM clinical data and as Blaine discussed, there were some discordant samples or at least Blaine discussed this category of samples where you may have DNA positivity and isolated core reactivity. Here we had core discrepant reactivity. Our test record was negative, but the PRISM test and anti-core test was positive.

Upon further testing, two our of three of these samples did have weak anti-HBs so they likely were from infected donors. Converse, we had one DNA positive sample that was PRISM negative and ortho positive and that sample was negative for all HBV serologic markers. So we know we had some discrepancies and one explanation for discrepancy

other than true HBV infection is false positivity of the DNA test perhaps due to carryover or sample contamination.

So we faced a reentry algorithm proposed such that we would have a follow-up or a clean sample and that sample would have to test negative for HBsAG, anti-core using a second licensed test. We included anti-HBs and an investigational or research HBV DNA assay. Subsequently at the BPAC discussion, the use of anti-HBs was discouraged. Next please.

So we formed the AABB TTD Task Force. We collected preliminary data that I will review from the Red Cross and sent it to FDA DETTD to request that the data that we collected were adequate to qualify a reentry algorithm. The FDA questioned the sensitivity of the DNA protocol and the study has yet to be completed because of the availability of PRISM reagents.

On May, 2003, we again met with FDA to propose a reentry algorithm which is comparable to the one today and I'll highlight the difference. Based on an eight week follow-up sample that test anti-core nonreactive preferably using a different test with comparable sensitivity but improved specificity and -- Next please.

The sample must test DNA negative and an assay that has a sensitivity of less than or equal to 10 copies per MIL. At that time we requested that IND tests could be used and that the next donation then could be used for transfusion if it tested nonreactive by all FDA required tests and the donor was otherwise suitable. We know now that the FDA requires the licensed DNA test for reentry and the qualification of that DNA test must use a licensed anti-core assay. Next please.

So the prepilot study that we did involved 3,000 anti-core repeat reactive unlike donations that were selected in 2001. The surplus NAT samples were contained in our NAT tube to limit contamination. The criterion for inclusion was nonreactive by all other test methods so we would have an anti-core only reactive.

There was no preselection of first time or two time anti-core repeat reactive donors. So we chose 3,000 to allow it to be robust enough so that we would include both one time and more importantly, two time repeat reactive donors. At the time of the study, our 2X anti-core repeat reactive rate was about 24 percent of Red Cross donors. So we could project how many were 2X anti-core reactive of the 3,000 to be

708. Next please.

The samples were tested individually with the NIG UltraQual 8-rxn test that has a 0.2 ml input. The definition of positive, that is the test is run in eight replicates. If any test is positive, the interpretation of the sample is positive. The sensitivity was 9 IU/ml and using NGI's conversion factor of an IU to a copy, it comes out to 31 copies per mil. Next.

So of the 3,000 tested, we had 0.63 percent samples reactive or 19. Eleven had less than 100 copies per mil low level as we know anti-core onlys have and of the eight reactions run, there was an average of only 1.7 reactions that were positive. We have another eight of the 19 with viral loads above 100 but not exceeding 500 with a mean of 287.5 copies per mil and here there was an average of 4.75 reactions of the eight that were reactive.

Data was provided to the FDA as I mentioned. FDA requested additional testing on the residual sample which has not yet been completed and the FDA stated that 31 copies per mil is an adequate sensitivity for anti-core donor reentry which is how we get to the 10 copies per mil or that is they want it sensitivity better than 31 knowing that commercial

tests were available to achieve this. So "since higher sensitivity DNA tests are available, it would be preferable to use such an assay instead." Next please.

So as I mentioned, the goal is to complete the study by looking at a second core test so that we could project the number of core nonreactives that would be eligible for reentry using this algorithm. The anti-core reactives would be investigated for anti-HBs and the assumption is that our 19 DNA positives would be PRISM anti-core reactive and we're in the process of getting this going. Next please.

If you put the study that I just described in context with other studies that have looked at similar types of data, we have 0.63 percent rate of anti-core positivity. The Roche clinical trials that were presented at the last BPAC had a 0.35 percent rate of anti-core only that were DNA positive and a study done by REDS had a little bit lower, a 0.24 percent. So this study still yields at the highest number of DNA positivity or one in 37,000. Next please.

Next, please.

So where are we now? We are under IND with NGI. The purpose of the IND is so that we can

use the DNA test as a counseling tool for anti-core repeat reactive donors. I mentioned there was no standardized confirmatory algorithm, so this would be one purpose of the study.

We would continue our survey of anti-core repeat reactive donations for HBV DNA reactivity, and, lastly, to limit viral loads and plasma pools for further manufacture, since anti-core reactives are included in frac plasma.

We rolled out the program earlier this year.

Next, please.

We used the eight-reaction test that I described for primer pairs used, each tested in duplicate, and, again, a reactive in an EVAY test is positive. Here we test in pools of 16. Positive pools resolve to the individual positive donation, and all positive samples are quantified.

Samples without adequate volume for pooling or resolution are tested individually. So we have a mixture of pool tests and individual tests.

The sensitivity of the pool test is the eight-reaction test with a 2 mL input -- this .9 IU per mL, or 3.1 copies per mL. However, when we have requalified with NGI, we have now found a three-fold

increase in sensitivity. So it's probably closer to one copy per mL sensitivity.

But in a pool, using the original validation data, it's about 50 copies per mL. When we do resolution testing, the resolution tests is about five copies per mL. And if we test a single unit, it's back to the 31 copies per mL that I mentioned for the qualification -- the pre-pilot qualification study. The quant assay has 100-copy per mL sensitivity.

Next, please.

All donors in this IND are notified of their test results, and they're deferred if they're even one-time or two-time core reactive and DNA positive. They're deferred if they're DNA negative but two times anti-core repeat active. And deferred donors are eligible for a followup study that we've just initiated, and donors will come back and be tested for all markers of DNA, but we won't do -- I shouldn't say "all." We won't do E and anti-E, at least at this point.

Next, please.

So how many donations have we tested to date? We've tested 6,006. This is now twice as large as the 3,000 pilot study I mentioned. .44 percent

anti-core is our reactive rate, but not all donations were available for PCR testing.

These are the outcome. About 60 percent were negative in pools. About another third of the donations were negative from positive pools. And of those that we were able to get one-time or two-time core data for, about 23 percent were two times anti-core repeat reactive donors.

Now, positives, we have 304, or 5 percent from positive pools, with another six samples that were positive and samples that were never pooled but tested individually. So we have a total of 310 positives of the 6,006, and this translates to about a 2.4 percent pool reactive rate.

Next?

If we separate out the 6,006 into HBsAg positive versus HBsAg negative, first, I'll go through the HBsAg positive. 179 of the 310, or just over half, were HBsAg positive. 99.2 percent was their mean HBsAg percent neutralization result, and they were all very high.

Viral loads ranged from below the limit of detection to five billion copies per mL. The median was 5,500 copies per mL. Eleven, or 6 percent, of the 179 had less than 100 copies per mL, but were

qualitatively positive.

Now, if we look at the data a little bit differently, if we just look at HBsAg positive samples from our database, about 97 percent, 96.7 percent, are anti-core repeat reactive. And of those, 96.4 percent of these HBsAg positive anti-core reactives were HBV DNA positive. So the data seem to all fit together as expected.

Next, please.

Now, with the HBsAg negatives -- and these would be the ones who potentially would qualify for reentry, we had 131 of 310. The viral loads were lower than the HBsAg positives, as you would expect, less than 100 to 6,400 copies per mL, and the median was lower than the limit of detection by the quantitative assay. 57 percent -- again, very similar to the pre-pilot data -- had less than 100 copies per mL but were qual positive.

Next, please.

So this graph shows you the distribution of the HBsAg positives by viral load, the HBsAg negatives by viral load -- again, these are all anti-core repeat reactive. The same data, just showing you the lower distribution of virus in the anti-core in the HBsAg non-reactive samples.

Next, please.

So, in total, 131 of 6,006 samples, or 2.18 percent, were anti-core repeat reactive only samples that were DNA positive. This is three and a half times higher than the pilot study which I showed you at .63 percent, and these two numbers are significantly different.

Why would we come up with a higher number now when the sensitivity, actually, by the original qualification data was actually less than the pilot study? I've listed some thoughts.

There has been no change, at least to the assay sensitivity. We have not changed the assay. However, upon revalidation of the assay, it did produce a three-fold increase in sensitivity the way the assay is run today at NGI. There were no changes to donor selection criteria. I mean, perhaps there's contamination in some of these samples. But from the way the data fit together with HBsAg, I don't think that's a high number. But our followup study will resolve the discrepancy.

And my last slide, please.

So, in conclusion, poor assay specificity and the lack of confirmatory test has led to the use of a two times anti-core repeat reactive algorithm

prior to deferral. But we know that donor return rate is low. Of those who return, two X anti-core reactivity is high, and the total successful donation yield then per year is low.

Anti-core reentry algorithms are projected to have higher yields if we switch to a new test with improved specificity. That should allow the validation or use of reentry algorithms with anti-core tests of improved specificity. A mass of anti-core repeat reactive donors demonstrates that .63 percent to 2.2 percent have HBV DNA, although the level of viremia is low.

So anti-core testing does have value, but mechanisms should exist to capture those donors that are lost.

Thank you.

ACTING CHAIRMAN ALLEN: Thank you very much, Dr. Stramer.

Quick question with regard to how these donors are handled the first time that they're found to be repeat reactive. What are they actually told?

DR. STRAMER: They're provided with a donor letter and a fact sheet that thanks them for their donation. We found repeat reactive on a test for anti-core -- you know, we explained the -- if you

tested abnormal on a test for hepatitis B virus, this does not mean that you're infected. And because of the high false positive rates of tests, you're encouraged to come in again and donate.

And then, we give them a little bit of a fact sheet that gives them risk factors and what you should do if you think you're infected with hepatitis B.

ACTING CHAIRMAN ALLEN: So they're told they can come back in eight weeks or --

DR. STRAMER: Correct.

ACTING CHAIRMAN ALLEN: -- or -- and when they come back in, it's not just for testing. They're coming back in to go through the donation process again.

DR. STRAMER: Correct. As any other routine whole blood donor.

ACTING CHAIRMAN ALLEN: So their testing process would be exactly the same in the mini pool as if they had never had an abnormal test.

DR. STRAMER: Correct. If their anti-core repeat reactive again, their donation will go to NGI. Correct.

ACTING CHAIRMAN ALLEN: Thank you.

Other questions for Dr. Stramer? This is

certainly a very important database. Yes?

DR. GOLDSMITH: I just wanted to ask two things. On the -- I thought I heard you say that the plasma from the units that were core reactive was used for further manufacture. Did you say that?

DR. STRAMER: Yes. Anti-core repeat reactive donations can be used for fractionated products, yes.

DR. GOLDSMITH: So the donor units that you collect are split. The cellular components are discarded.

DR. STRAMER: Correct.

DR. GOLDSMITH: And the plasma is used for further manufacture.

DR. STRAMER: Correct. And that's to maintain anti-HBS levels and factor -- you know, fractionated products.

DR. GOLDSMITH: And I just have kind of a philosophical question about the practice of medicine. When these donors present and have a reactive test, if I understand what you said correctly, they get a letter indicating that they should come back to the donor center to donate again. Are they referred to physicians for medical follow up or --

DR. STRAMER: Well, we --

DR. GOLDSMITH: -- care or individual testing, to try and sort out what their status is?

DR. STRAMER: Well, we -- firstly, the letter is pretty generic. And it says, "You've tested with -- you have an inconsistent test result. If you'd like more information, please call the Blood Center." But we explain what test they were used and -- what test they were found reactive. And because of the high rate of false positivity in this particular test, you're eligible to donate again.

But if you have risk factors, you know, we encourage you not to donate -- and those are listed on the attached fact sheet. So we go through, you know, typical information about hepatitis B, who is at risk, what to do if you're at risk, if you believe at risk or you're unclear about the meaning of these test results, please see your physician.

So they are referred to the medical system, but they are -- they are told that they can come back and donate. And if found non-reactive, their donation will be used.

ACTING CHAIRMAN ALLEN: Dr. Hollinger.

DR. HOLLINGER: Susan, a couple of questions, and you may not know the answer to these.

DR. STRAMER: More questions than you've

sent me on e-mail?

DR. HOLLINGER: Huh?

DR. STRAMER: More questions than you've sent me on e-mail?

(Laughter.)

DR. HOLLINGER: Yes. Sorry about that.

DR. STRAMER: That's okay.

DR. HOLLINGER: Just one question about -- you mentioned that there were 97 percent of the HBsAg positives or anti-HBC repeat reactive. So there's 3 percent that were not anti-HBC reactive, repeat reactive. Were HBV DNAs done on those three? I mean, on that 3 percent? And how positive were those HBS antigens on those 3 percent in terms of ratios?

DR. STRAMER: You'll have to come to my AABB presentation where I discuss those data. The 3 percent are not part of the IND. The IND specifies only anti-core repeat reactive donors who tested.

The HBsAg's confirmed positives -- now we have switched back from the Ortho test to the Abbott test -- they split into two groups. Clearly, there are false positive neutralizations that have low signal to cutoff ratios, and lower percent neutralization values. Although about 60 percent still have greater than 80 percent neut vales, they're

a large proportion of this half that we believe are false positive have low percent neuts.

So it's really mix -- a mixture of both positive and negatives. If we were to do DNA testing on this, this would obviously resolve this, or if we were to do donor followup. But we have not pursued that for these 3 percent.

DR. HOLLINGER: The other thing -- again, you may not have the data. But, again, of those that are anti-HBC positive but, say, PRISM negative, what's the HBV DNA in those? That were -- the previous tests that are repeat reactive anti-HBC positive that turned out to be negative by another test -- let's say PRISM test -- what -- were those looked at for HBV DNA?

DR. STRAMER: The only one -- well, the only time we had that discrepant population was in the PRISM clinical trial. And I said we had one of those that was Ortho test of record reactive and PRISM non-reactive. But it turns out that that donor was not HBV infected. We did get donor follow up for that particular donor.

DR. KUEHNERT: First, just a clarification on the sensitivity. So with the pooled method you get a sensitivity that's significantly higher than with the single unit detection method. Is that right?

DR. STRAMER: Significantly lower.

DR. KUEHNERT: I mean, it's --

DR. STRAMER: It's less sensitivity.

DR. KUEHNERT: Yes. So the -- so, for instance, for single unit you said it was 31 copies per mL sensitivity versus pools of 16, 3.1 copies per mL?

DR. STRAMER: No. No. That's -- 3.1 is the test sensitivity. But then, when applied to a pool of 16, I said the pool sensitivity in copies per mL was about 49.5 copies.

DR. KUEHNERT: Oh, okay. Okay. Thanks for that. And then --

DR. STRAMER: But that 49.5 -- you know, it depends if you look at -- NGI filed an IND. And in that IND, they have the .9 or 9 IU per mL, which I reported. But then, before we did the study and the way that we all operate, I wanted to revalidate their test and look at even a more sensitive test. So instead of doing an eight-reaction test, I wanted to use a formula input and use a 16-reaction test.

So we, then, had to requalify tests of record. And at that time we got a three-fold increase in sensitivity of the NGI method. So it may be 50 divided by 3 is the operating sensitivity of the

assay.

DR. KUEHNERT: Susan, it confused me, because then it became more sensitive than the single units. That was -- okay. That clarifies that.

DR. STRAMER: Yes.

DR. KUEHNERT: The second question I had was about the 75 samples that were less than 100 copies per mL but qualitatively positive. And maybe I missed this, but what -- are you able to quantitate what those are in any way?

DR. STRAMER: Well, linearity of the NGI quant assay, or their standards only go down to 100 copies per mL. So the qual assay, which runs at much more sensitive, you can have a qual positive sample that you can't quantify, because the viral load is too low.

Now, I haven't pushed NGI with more standards, but certainly, as one of their largest customers, that could be done. And it's an issue, because many times, not only for HBV but HIV/HCV/West Nile, we can't get quants less than 100.

DR. KUEHNERT: That would be useful.

DR. STRAMER: Yes. I agree.

DR. KUEHNERT: Thanks.

DR. EPSTEIN: I have two questions, Sue.

You noted that among first-time donors with a one-time reactivity anti-HBC their rate of a second reactive anti-HBC was 88 percent, whereas for repeat donors, or previously repeat donors, in a comparable situation there was only 38 percent. That tends to suggest that the true positive rate is higher for the first-time donors. Was that borne out with the DNA data? Did you stratify that? I may have missed it.

DR. STRAMER: No. I haven't done that yet, but it's certainly interesting.

DR. EPSTEIN: So it's an interesting question.

DR. STRAMER: That's right.

DR. EPSTEIN: Okay.

DR. STRAMER: That's right.

DR. EPSTEIN: And then, the second question that I have -- I've noted that in your histogram, where you showed the viral loads for --

DR. STRAMER: Yes.

DR. EPSTEIN: -- the HBsAg negative population and the HBsAg positive population, the histogram is bimodal for --

DR. STRAMER: Yes.

DR. EPSTEIN: -- viral load and antigen positives. And can you comment on whether there's an

explanation for that?

DR. STRAMER: No. I haven't delved into -- into that yet, but I noticed the same thing. And there has to be some explanation for that. I just haven't had time to -- to determine --

DR. EPSTEIN: I was wondering whether that distinguished maybe acute versus chronic infections, but --

DR. STRAMER: Right. Right, right. I -- yes. But --

DR. EPSTEIN: Okay. Thank you.

DR. STRAMER: -- early acute when they're anti-core reactive versus lower level carriers. Yes, we haven't -- well, we haven't gotten there yet.

DR. EPSTEIN: I was just curious.

DR. STRAMER: Yes.

DR. EPSTEIN: Okay. Thank you.

ACTING CHAIRMAN ALLEN: Dr. Strong.

DR. STRONG: Just a comment. Most of this data has been presented with the Ortho anti-core assay, although, as Sue has said, they have now shifted back to Abbott for other reasons. But in the clinical trial with Roche, the repeat reactive rate with the Abbott assay was about double Ortho's. So I think their false positive rate is quite a bit higher,

and there is still a lot of centers using the Abbott anti-core. Everybody is waiting for PRISM to be approved.

The question I have, Sue, do you have any cases in which you have a surface antigen positive that is negative for core and DNA?

DR. STRAMER: Because we haven't tested the HBsAg only for DNA, I can't answer that question. We know the HBsAg confirmed positives do distribute into two clearly definable groups -- those that have high ST -- just like HIV, those with high STCOs that confirm strongly in confirmatory tests, and those that are weakly reactive on EIA screen and don't neutralize to the same extent as this high EIA population does.

So what we would -- what would be interesting is to know how DNA segregates in those populations.

ACTING CHAIRMAN ALLEN: Okay. From the floor microphone, would you please introduce yourself for the Recorder?

DR. TABOR: I'm Ed Tabor from FDA. I think it's important -- by the way, Sue, I'm always impressed by the scope of your research.

I think it's important at this point to say that the anti-core test was originally developed

in the Bureau of Biologics, the forerunner of CBER, by Drs. Lewellis, Barker, and Dr. Robert Garrity, as a result of basic untargeted research. And it came out of this serendipitous observations resulting from an attempt to see what would happen if you gave cytoxan to a chronically infected chimpanzee.

Now, I state this because in the previous discussion one of the panel members said something about the reagents coming from chimpanzees in the older tests. There's no question that the original research tests used chimpanzee reagents, but I'm -- I couldn't be wrong, but I don't recall that any of the licensed assays use chimpanzee reagents.

And I think there have been changes in this test configuration over the years, but basically most of the tests have been competitive inhibition assays, and that's been one of the problems with this test and particularly with regard to its specificity.

DR. STRAMER: May I add something to Dr. Tabor's comment? The two tests used -- one is a competitive inhibition test, and the other is a direct anti-globulin test. And the anti-globulin test is the test with the improved specificity.

ACTING CHAIRMAN ALLEN: Thank you for that historical perspective. I think too often we don't

spend enough time looking back at the history of some of these issues, and that was important.

Yes, Dr. Kleinman.

DR. KLEINMAN: Steve Kleinman. I just wanted to comment on one of the issues raised by the panel member about what are the deferral policies currently for anti-core positive donors. And we heard the ARC deferral policy, which is to follow the FDA guidelines and defer after two times and notify the donor after one time. But there's great variability in what other blood centers do.

Many blood centers will defer the donor, or have up until now, deferred the donor after a first time anti-core, basically because they haven't thought that it was worthwhile to allow people to come back a second time.

Secondly, some blood centers have actually on their own decided to, in addition to doing the anti-core assay test of record, they would do a second manufacturers' anti-core assay and/or an anti-HBS assay, and the notify donors based on several different results and stratify their notification message to say there's a greater probability that you may have been infected, that this is a real result, or there's a greater possibility that you're a false

positive.

So we don't have uniformity of practice in terms of how we implement donor deferral for anti-core or how we actually go about notifying persons.

DR. HOLLINGER: I like what Sue does when she -- on some of her slides will show a quotation around anti-core only, just to make it clear that many of these have not been tested for anti-HBS, anti-HBE, or other hepatitis B markers. And I think that's a good way of doing it, so that we're not thinking that anti-core only means just nothing else there.

DR. BUSCH: Hi, Sue. Just a question. The increasing rate of DNA in --

ACTING CHAIRMAN ALLEN: Would you introduce yourself, please?

DR. BUSCH: Sorry. Mike Busch from Blood Systems. In your recent data compared to the earlier, could that relate to the anti-core test that was employed? Was your earlier work with the Abbott in the more recent drive for --

DR. STRAMER: No. The entire data set, as I showed, since 1995 we have been using the anti-core Ortho test, actually since earlier than that. So the second or third slide I showed with the anti-core rate shows over nine years of anti-core Ortho repeat

reactivity. And the entire data set also includes Abbott HBsAg. It was post our conversion from Ortho 3.

ACTING CHAIRMAN ALLEN: Dr. Strong.

DR. STRONG: I might just add to the complexity of what Dr. Kleinman just mentioned that there is also some centers that are doing DNA. So it really goes all over the map.

DR. STRAMER: Right. That's why I mention there's no standardized confirmatory algorithm. And you seconded it and thirded it.

ACTING CHAIRMAN ALLEN: Dr. Schreiber.

DR. SCHREIBER: Sue, have you made any estimate of what the capture would be of reentry of donors, deferred donors? I did just a back-of-the envelope and it doesn't seem to me that it would be very big based on the million donors that seem to be deferred over a 17-year period. It seems to me that you'd only get somewhere around 100,000 units a year maximum from -- if you reinstate donors, or less.

DR. STRAMER: Well, I think you have to look at reentry, generically, really has two purposes -- one, to allow donors who truly believe that they want to give to have that ability to give; and, secondly, but of more frequently less consequence, is

an increase to the blood supply, because we're reentering donors.

The yield of reentry for any marker is not high, and certainly is -- if we went back to 1986, to those donors we initially deferred because of corzine, you know, one, would we even be able to contact them? And after 18 years, you know, they'd look at us cross-eyed. You've finally done something about our anti-core false positivity? That's not a very good message from the blood centers.

So it really is proportionate to the amount of time, or inversely proportionate to the amount of time that the donor has been deferred. So we likely would start, as we have with other reentry protocols with the most recent deferrals and work our way backwards.

But you're right, George. Any -- you know, one of these reentry have huge yields, but just the ability to do it for those donors. And if any marker we do reentry for, certainly anti-core has the greatest catchment.

Okay. Thank you.

DR. STRONG: I'd like to say "only 100,000 donors." For a blood center, that's a lot of donors.

DR. SCHREIBER: But then you have to

divide by three, because her rate was for three years.

DR. STRONG: But you'll also notice that in her data set she has some donors that donated 57 times. Those are the ones -- those dedicated donors are the ones we'd like to have back.

DR. STRAMER: Well, it's an emotional issue more than anything. I mean, probably more than anything else.

ACTING CHAIRMAN ALLEN: Thank you.

We'll move on to our next presentation in this section, which is studies of deferred donors. Thomas Clement from Roche Diagnostics.

DR. HERMAN: Okay. I'm Steve Herman. I'm not Tom Clement. And I'm going to speak about a small study we did to look at the potential application of the COBAS AmpliScreen HBV assay, which is currently under review, and the reentry algorithm for donors deferred for anti-core reactivity. And this study was conducted by Guy Tegmeier at the Community Blood Center of Greater Kansas City, with Yungfin Yang and Jim Glarda from Roche.

So Dr. Kaplan reviewed the history, so I'll just go through it very quickly. The anti-core antibody test was introduced in the United States in 1987, and, in 1991, the test was licensed for blood

screening. And over the past 16 years it's estimated that the components from up to one and a half to two million donations have been discarded due to anti-core reactivity. And testing -- testing with the second license test has shown that a large fraction of them are likely to be false positive.

So what are the -- there's a reservoir of donors that exist that could be reentered if there was an algorithm. And with the licensed assay of greater specificity, and the availability of sensitive nucleic acid amplification tests, the tools for reentry algorithm may now be available, or may soon be available I should say.

So here's the current algorithm for how donor and product management decisions are made with regards to anti-core reactivity. Donations tested for anti-core antibody, and if the donation is repeatedly reactive -- and it's the first time that that has been observed -- the products are discarded, but the donor remains eligible for repeat donation.

If the donor comes back and is again repeat reactive for anti-core antibody, the products are discarded and the donor is deferred. And the challenge is to identify a reentry algorithm that maximizes the recovery of those donors without posing