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AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

68TH MEETING

Thursday, March 15, 2001

8:00 a.m.

Hilton Gaithersburg
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Gaithersburg, Maryland

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Paul R. McCurdy, M.D.

SPEAKERS

Michael P. Busch, M.D., Ph.D. (3-15)
Jed B. Gorlin, M.D. (3-16)
Monica Parise, M.D. (3-16)
Susan Stramer, Ph.D. (3-15)
Cees van der Poel, M.D. (3-15)

GUEST

David Wright, Ph.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

DR. SMALLWOOD: Good morning. Welcome to the 68th 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 both days of this meeting.

Statement of Conflict of Interest

The following announcement is made part of the public record to preclude the appearance of a conflict of interest at this meeting. Pursuant to the authority granted under the Committee Charter, the Director of FDA's Center for Biologics Evaluation and Research has appointed Dr. Paul McCurdy as a temporary voting member.

To determine if any conflicts of interest existed, the agency reviewed the submitted agenda and all relevant financial interests reported by the meeting participants. As a result of this review, the following disclosures are being made.

In accordance with Title 18, United States Code 208, Dr. Kenrad Nelson has been granted a waiver which permits him to participate fully in the committee discussions. In addition, Dr. Raymond Koff has been granted a limited waiver for the discussion on NAT for hepatitis C and HIV and the discussion on blood bags for diversion of initial collection. This waiver will permit him to

participate in the discussions of these two topics but not vote.

The following participants have associations with firms that could be affected by the committee discussions: Drs. Boyle, Chamberland, Fitzpatrick, Kagan, Knowles, Linden, Macik, Schmidt, Simon and McCurdy. However, in accordance with our statutes, it has been determined that a waiver and appearance determination or an exclusion is not warranted for these deliberations.

With regards to FDA's invited guests, the agency has determined that the services of these guests are essential. There are reported interests which are being made public to allow meeting participants to objectively evaluate any presentation and/or comments made by the participants.

Dr. Michael Busch is employed by the Blood Centers of the Pacific. He receives speaking fees from Chiron, Roche and Gen-Probe. Dr. Busch has a contract with Chiron and Gen-Probe for laboratory work supporting clinical trials of NAT, a contract with NHLBI involving NAT assays and a grant with Roche to develop KPCR assays. Dr. Busch worked with Alpha, The American Cross, Chiron, Gen-Probe, Roche, The American Blood Centers, Bayer and Aventis in the evaluation of NAT testing issues.

Dr. Jed Gorlin is employed by the Minneapolis

Blood Center. Dr. Monica Parise is employed by CDC. She collaborated on a scientific publication with an employee of the Community Blood Center of Greater Kansas City involving U.S. malaria surveillance data.

Dr. Susan Stramer is employed by the American Red Cross. The American Red Cross uses Gen-Probe products distributed by Chiron for NAT screening. Mr. David Wright has a financial interest in a firm that could be affected by the discussions.

In the event that the discussions involve other products or firms not already on the agenda for which FDA's participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and 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 any current or previous financial involvement with any firm whose products you wish to comment upon.

Copies of waivers addressed in this announcement are available by written request under the Freedom of Information Act.

Are there any declarations that anyone would desire to make, committee members, anything that may have

been omitted?

Hearing none, at this time, I would like to introduce to you the members of the Blood Products Advisory Committee.

First, I would like to introduce the new committee chairman, Dr. Kenrad Nelson, who is from the Johns Hopkins University School of Public Health. Some of you may know that Dr. Nelson previously served with the Blood Products Advisory Committee, and we are glad to welcome him today.

We also have the addition of a new member, Dr. Raymond Koff, from the University of Massachusetts. Dr. Koff is an expert in hepatic diseases and infectious diseases.

We also have the extension of our member, Dr. Jeanne Linden. Dr. Linden, raise your hand. Thank you.

The other members I will introduce starting on my right, going around the table. Dr. Toby Simon, Dr. Paul Schmidt, Dr. Sherri Stuver, Dr. David Stroncek, Dr. Gail Macik, Dr. John Boyle, Dr. Mary Chamberland, Dr. Fitzpatrick, Dr. Richard Kagan, Dr. Marion Koerper, Dr. Mark Mitchell, Mr. Terry Rice, Ms. Kathy Knowles, Dr. Paul McCurdy.

Absent for this meeting are Dr. Norig Ellison and Dr. Daniel McGee.

As you may notice, we have a full agenda for this

morning. We would ask that all the participants and speakers please adhere to the instructions coming from your chairman. I know he is going to be very intent on getting us through this meeting.

At this time, I would like to turn over the proceedings of the meeting to the chairman, Dr. Kenrad Nelson.

Thank you.

Welcome and Opening Remarks

DR. NELSON: Thank you, Dr. Smallwood.

It is a pleasure to be back with the committee. I think this is an important committee and it has been of interest to me as a non-blood banker to learn from the presenters and the other members of the committee.

The first topic today is comparative sensitivity of hepatitis B NAT and hepatitis B surface antigen including increased sensitivity of new surface antigen kits or reagents.

The first speaker will be Dr. Ed Tabor from the FDA.

Comparative Sensitivity of HBV NAT vs. HBsAg

Introduction and Background

Edward Tabor, M.D. IOD, OBRR

DR. TABOR: Good morning. In the first half of the 1970s, the blood and plasma communities moved quickly

from having no licensed screening tests to detect hepatitis B virus to having highly sensitive radioimmunoassays that were licensed and whose use was required.

These radioimmunoassays were about as sensitive as many of today's enzyme immunoassays. Everyone was really pleased to have eliminated 90 percent of the cases of post-transfusion hepatitis. Most of the remaining 10 percent were not due to hepatitis B virus.

The dramatic elimination of most HBV cases made it possible for most people to accept the fact that the new technology, in other words, the radioimmunoassay, just could not eliminate 100 percent of HBV cases. For instance, as of 1996 to 1998, a much later date, it was estimated that 1 in 63,000 volunteer whole blood donations that were negative for HBsAG and anti-HBC would still transmit hepatitis B virus to the recipient due to the presence of undetected HBV.

The prevalence of infectious HBV in paid plasma donations that were negative for HBsAg was estimated at that time to be 1 in 18,000. These, however, would not transmit HBV because the plasma is used to make products that are now subjected to procedures to remove and inactivate HBV.

In the late 1980s, polymerase chain reaction assays were developed. By the late 1990s, the concept of performing these and other nucleic acid amplification tests,

or NAT, on many pools of blood or plasma was developed. This made it practical to screen blood and plasma despite the fact that NAT methods were still inherently labor intensive and expensive.

Minipool NAT for hepatitis C virus and for human immunodeficiency virus, type 1, were being conducted under investigational exemptions or INDs on virtually all units of plasma collected in the United States and on greater than 95 percent of units of whole blood by the end of 1999.

Although initial efforts to implement NAT screening had focused on screening for HCV and HIV, pressure to begin NAT screening for HBV had been growing due to interest in HBV NAT screening in other countries.

For instance, Japan had been requiring HBV NAT screening of whole blood donations since October 1999. Government and industry in both Japan and Germany had expressed interest in screening plasma including plasma imported from the United States by HBV NAT.

Preliminary testing showed that the rate of detection of HBV by NAT screening of minipools was higher than expected with detection of HBV DNA in minipools of HBsAg-negative source plasma, reported at an FDA workshop in December 1999, at 11 of 43,000 donations in one study and 56 of 3 million donations in another study.

At that December 1999 workshop, one of the

scientists present suggested that the newer, more sensitive HBsAg tests, when applied to individual donations, might provide screening sensitivity equivalent to HBV NAT on minipools or possibly even more sensitive screening than that provided by minipool NAT testing.

At the present time, all licensed screening tests for HBsAg are required to detect samples with a designated minimum concentration of HBsAg in the FDA lot release panel prepared and maintained by the Center for Biologics Evaluation and Research.

The cutoff for that panel represents so-called third-generation sensitivity and it was set based on the sensitivity of the available technology some years ago, a level of sensitivity that has continued to be appropriate to current technology up until now.

Minipool NAT screening for HBV would have to be very sensitive to be useful if the more sensitive HBsAg tests were used. In addition, of course, if the cutoff for passing the lot release panel were set at a more sensitive level, it would force all manufacturers to achieve the same level of sensitivity in their HBsAg tests as found in the newer tests if they wanted to continue to be permitted to market their tests.

Several HBsAg screening tests that either have been licensed recently or in the advanced stages of review

for licensure are so sensitive that only donations containing fewer than 1,000 HBV DNA copies per mL or perhaps even fewer copies would fail to be detected. In fact, these tests are at least one order of magnitude more sensitive than the other licensed HBsAg tests. Obviously, the new tests exceed the sensitivity required to pass the lot release panel.

By calculation, these tests are as sensitive as an HBV NAT conducted on a minipool in which the minipool was as small as 20 samples if the NAT had sensitivity at a level of 50 copies per ml. In fact, HBV NAT sensitivity as low as 10 copies of HBV DNA per mL has been reported.

Calculations like these, as well as other modeling strategies, can be used to evaluate the relative sensitivities of HBV NAT done in minipools and HBsAg tests done on single donor samples, however, definitive data on the relative sensitivity of the two systems would require a head-to-head comparison in evaluating the same samples with each.

We have designed and conducted such a study. A coded panel was created consisting of 128 samples. These consisted of 100 serial plasma samples from among 10 commercially available seroconversion panels, in other words, from 10 patients. The remaining 28 samples consisted of control samples from the FDA lot release panel, also

dilutions of the WHO HBV DNA international reference standard and others.

All seroconversion panel samples and controls were vialed in identical containers, interspersed and coded. Some duplicates were included to test assay consistency. Seven HBsAg test methods were done on the coded panel, all licensed tests or pending licensure.

HBsAg tests were done by the FDA lot release laboratory whose staff and director had no knowledge of the code. Samples were tested by NAT on minipools by two plasma fractionaters and two manufacturers involved in the collection and processing of whole blood and its components, each according to a procedure in their IND for the creation of minipools and testing.

Since these NAT methods are all procedures that are currently under INDs, they may or may not be identical to the procedures that become licensed in the future.

I would like to acknowledge the contributions of the follow individuals to the design phase of this study. It has been a pleasure to work with them. These are Dr. Michael Busch, Dr. Robin Biswas, Dr. Chu-Chieh Hsia, Mr. Jimmy Kim, Dr. Peter Lauchenbruch, Dr. Charles Roberts, Dr. Paul McCurdy, Dr. George Nemo, and Dr. Indira Hewlett.

Dr. Busch is going speak on another aspect of this study and following that, Dr. Biswas will present a

preliminary analysis of the results from the laboratory portions of the study.

DR. NELSON: The next speaker is Dr. Michael Busch from Blood Centers of the Pacific.

Michael P. Busch, M.D., Ph.D.

DR. BUSCH: Thanks, Ken, and thanks.

[Slide.]

What I am going to do is to sort of introduce our understanding of HBV infection by presenting data that was actually presented at last year's AABB meeting on the dynamics of HBV viremia in the pre-surface antigen phase.

This analysis, as you will see, is focused on 23 seroconversion panels from Alpha that were the basis for the selection of the 10 panels that Ed alluded to. Actually, I think the second presentation will be by Sue Stramer who will present a similar, but a different panel set in a slightly different modeling strategy. What Robin will present later is the actual empirical direct analysis of the currently available surface antigen and NAT systems on the panels.

[Slide.]

This study was conducted under the context of what we call the NAT Study Group, which is a collaborative program that includes the major blood organizations. It is coordinated through the REDDS program with NHLBI support.

It involves liaisons from FDA and CDC, and then a number of industry collaborators including the major NAT manufacturers, as well as a number of the plasma manufacturers and testers related to the plasma industry.

[Slide.]

Now, with respect to HBV NAT, as summarized by Ed, there is interest in introducing HBV NAT coming both from the plasma industry, where there is a mandate to introduce HBV NAT in order to derive recovered plasma that can be further fractionated.

In addition, we have over the last several years seen several European and Japanese have introduced HBV NAT for whole blood screening, so there is a precedent out there that is clearly driving the U.S. to consider incorporating HBV into regular blood donation screening.

Now, the issue of how much will derive from introducing HBV NAT or the yield is related to obviously the sensitivity of the surface antigen tests and whether or not one is doing anticore screening. In the U.S., in the whole blood sector, we screen with anticore, and therefore, the entire benefit of NAT will be at the front end window phase, the pre-surface antigen period.

In other countries, for example, throughout Europe, anticore screening is not routine. Likewise, in the U.S. source plasma industry, it is not performed, and

therefore, a significant yield of HBV NAT is actually in persons who are chronic carriers in whom the surface antigen levels have declined below detectable levels, but those people in the whole blood sector here are detected by anticore, so this is not an issue.

So, again, our focus here really is the front end window phase. In that context, the critical predictor or determinant of yield, the second critical determinant is the incidence rate or the rate of new infections, how many donors are actually going through that early pre-surface antigen viremic phase.

The other parameter in terms of NAT detection is the sensitivity of the HBV DNA assay and whether it has performed either on neat samples or on minipools, which the dilution factor of minipools basically reduces the sensitivity, but the critical missing piece that we have worked up now is the dynamics of HBV ramp-up, and that is what I am going to show now.

[Slide.]

The objectives of this study were to characterize the dynamics of HBV viremia in the pre-surface antigen phase, and then based on the understanding of that ramp-up phase, we can derive a model that estimates how much window period closure could be obtained by introducing minipool or individual donation NAT assays using some preliminary

estimates of what the sensitivity of those tests would be relative to, in this study, a single prototype sensitive HBsAg test.

Once we know the window period closure, we can use the incidence data from the REDDS group to estimate the yield by just factoring the window closure times the incidence rate.

[Slide.]

In this study, we identified 23 plasma donors, again identified by Alpha Therapeutics, who had seroconverted to HBsAg, and these persons had been previously characterized actually by HBV DNA by Lorraine Peddada and colleagues at NGI using NGI's both qualitative and quantitative assays, and we derived estimates for both the frequency of detection, a very low level viremia, by the qualitative testing, what we call the pre-ramp-up phase, which I will define, and then we use the quantitative data to estimate the doubling time for each panel as a composite.

These seroconverters had actually been originally detected through their routine screening at the Alpha laboratory by the Genetic System surface antigen test, and in the analysis, we actually used the Abbott Prism data derived using the European, a previously widely used protocol, to estimate S to CO at each donation and understand the relationship between surface antigen

evolution and viral load.

We assumed that individual donation NAT could achieve either 5 or 50 genome equivalent per mL, 50 percent hit rates, and that minipool NAT would be running at about 1,000, essentially a 20-fold dilution of the 50 genome sensitivity assay.

[Slide.]

The analysis was conducted by David Wright, who works with Westat and is here. This involved what is called a bivariate longitudinal regression model, which was used to estimate the HBV doubling time or the production rate during the ramp-up phase, as well as could be used to calculate the HBV concentration at the cutoff level or the lower limit of detection of the assay that we were evaluating, again, in this specific study, the Prism HBsAg European protocol.

Then, we could estimate the pre-surface antigen window closure based on the doubling time and the assumed further reduction in detection by minipool or individual donation NAT, and then again project the yield using the REDDS incidence of 5.1 per 100,000 person years.

[Slide.]

This just illustrates one of these panels, actually, a relatively simpler panel. You can see here day zero is set as the day when this particular plasma donor was first detected as HBsAg positive based on the test of

record. What you are looking at here are previous time points ranging out to minus 37 days, and you are looking in the bars at the HBV DNA load data. This line is the Prism S to CO results.

So, you can see that in this particular panel, there is a clear log linear ramp-up, log increase in viral load relative to time during this phase here that precedes detection of surface antigen by about two or three weeks.

So, it is this kind of data here that a regression analysis could yield an estimate of the doubling time, and this is what we term the ramp-up phase, but in addition, in a large number of these panels, prior to the ability to quantify HBV viral load, and during the period where viral load is clearly increasing over time, you can detect HBV DNA.

In many of the panels you can intermittently detect it, where the viral load is very low, sometimes quantifiable at 100 copies, sometimes positive, but nonquantifiable, and then it will go negative, then positive, and then eventually, you will reach the ramp-up. So, we term this the pre-ramp-up phase, this period that in some panels extended back a month or more during which one intermittently detects very low-level HBV DNA, and reproducibly detects it.

[Slide.]

This is a graph of the doubling time data for these panels, and you can see a splay of curves here representing the increasing viral load over time for each of these panels, and then the red line represents the regression line, that in essence summarizes the average ramp-up rate for all of these panels.

[Slide.]

In this slide, you can see the HBV DNA regression line, and a similar line can be derived in this case for the one surface antigen test we evaluated. In the subsequent study that Dr. Biswas will present, there is a regression line for all seven surface antigen tests.

You can see that during this pre-seroconversion or ramp-up phase of HBV infection, that these lines parallel one another, that the surface antigen and DNA load are really very closely related to one another over time, indicating that during this phase of infection, that all of the HBV circulating particles or material are probably Dane particles or appropriately representing a DNA copy per particle and a relevant level of surface antigen.

As you all know, in chronic carriers, this relationship becomes perturbed and the liver cells put out large amounts of surface antigen in great excess of HBV DNA, so this would be a very different relationship if one looked at samples from chronic HBV carriers, but in the window

phase, there is a very tight relationship between surface antigen and DNA.

Now, both of these lines essentially parallel one another, and the slope is approximately 0.1 log genome equivalent per day, which then translates out to a doubling time of 2.84 days. So, HBV DNA and antigen increase in the plasma, doubling approximately every 3 days. This is dramatically slower than with HIV or HCV, which double in the plasma every half to 1 day, so a very slow ramp-up virus relative to those other two viruses.

[Slide.]

This just illustrates how we can now use this model or the computer understanding of the relationship between DNA and antigen to ask the question of interest to us today. I am just going to walk you through this to illustrate how this is done, but the truth is this is actually done through David Wright's programs, and he derives these numbers with confidence bounds, as I will show you.

So, one question, for example, is with the prototype surface antigen assay that we evaluated, the Prism, what is the cutoff level of viral load. So, to ask that question, we basically look at the log of the S to CO relationship, and the log of 1, which is an S to CO of 1, the cutoff is zero.

So, we walk across that zero line and identify at what time point does the HBV surface antigen test break cutoff, and then we go up and ask what is the viral load at that time point, and the answer in this analysis is approximately 3,000 genome equivalents of HBV DNA are present at the cutoff limit of the HBsAg test.

Then, we can ask the question, okay, well, what if we introduce the test that had a sensitivity of 1,000 genome equivalents, such as we predicted minipool might achieve, and then we can simply walk back on this curve and down, and then understand the time interval between when the surface antigen test would become positive and when an HBV NAT minipool would become positive.

So, this is the way visually you can sort of walk through these curves.

[Slide.]

This just asks the further question of how much further window closure would be obtained with a test that had a 50 or 5 genome equivalent HBV DNA load sensitivity, and again we can come back and walk down to the time line and say that that would close the window by about 15 days to 30 days. So, you can basically visually understand how these relationships between DNA load and surface antigen can be translated into estimated window period closures.

[Slide.]

In summary, in terms of the major findings, then, we had a surface antigen load at cutoff estimated at about 3,000 for this prototype assay. The mean doubling time was about 2.84 days.

In terms of this pre-ramp-up viremia, there were actually 10 panels that had samples extending back greater than 3 bleeds prior to ramp-up. Interestingly, in those 10 panels, all 10 demonstrated low-level intermittent viremia detected often nonquantifiable up to 3 months, from 10 days to 3 months preceding ramp-up viremia.

So, this phenomenon of smoldering pre-ramp-up viremia seems to be quite common in HBV.

[Slide.]

This is really the key projections of the model then, so we are asking the question of what would be the projected window closure and yield of adding minipool or HBV NAT to this surface antigen test. Again, the surface antigen test in question was estimated at having about a 3,000 genome equivalent per mL.

So, adding a minipool NAT that had 1,000 genome sensitivity was predicted to close the window by about 4 1/2 days, and based on the incidence rate, that would predict to yield about 6 infected HBV window phase donations per 10 million donations. As all of you I think know, we have about 12 to 13 million donations per year, so perhaps 7 or 8

infected donations per year would be detected by minipool NAT that were surface antigen negative.

Going to an individual donation, NAT with 50 copy sensitivity, was estimated to reduce the window by 17 days and yield approximately a 23 per 10 million infected window phase units. In an assay that could achieve 5 genome equivalent sensitivity, would close the window by 26 days, yielding 36 per 10 million.

So, these are the predicted window closures and yields based on the model. Again, you will see data later from Dr. Biswas that will actually evaluate the accuracy of these predictions.

[Slide.]

Just a brief summary. These is actually an update of the summary slide at the AABB. One of the things we felt we needed to do is actually conduct a direct comparison of bona fide or currently under development or existing minipool and individual donation NAT versus representative surface antigen test, and this study is now done and will be presented by Dr. Biswas.

We were also interested in understanding the infectivity of these very low level viremic ramp-up samples and pre-ramp-up samples, and a study is under design with Dr. Harvey Alter to look at this in an animal model.

We also felt it was important to understand the

relative cost effectiveness of HBV NAT versus the other viruses because, as you all know, HBV typically in adults certainly is a relatively benign and transient infection, so we have now looked at this, and I want to present a little bit of data on this.

The other issue is if we do bring forward HBV NAT, what will be the implications about the need to retain surface antigen or anticore. I am not going to go into that.

[Slide.]

Just a few slides to sort of put into broad context and lead into a little bit of data on sort of the cost effectiveness and particularly the comparative cost effectiveness of HBV and clinical implications of HBV prevention versus HIV and HCV.

This is a collaboration with Jim AuBuchon and one of his associates, Brian Jackson. This just is the baseline sort of window period data for each virus that you are all very familiar with. This essentially is data from the Schreiber paper that estimates the window period of about 20 days for HIV, about 70 for HCV, 45 for HBV. Minipool NAT can close these as indicated, and then single donation NAT would leave us with this theoretical pre-viremic phase, the so-called eclipse phase, which the infectivity of this phase is a matter of current research.

[Slide.]

This slide just summarizes given these residual window periods and the known incidence rates, this summarizes the estimated risk per unit before and following minipool NAT and then following individual donation NAT.

I am not going to go through this, I think you all have this as a handout, but basically, the focus on HBV, you can see that we are currently estimating a risk of around 5.5 per million, which would drop with minipool NAT fairly modestly to 4.8, because the window closure with minipool is going to be very modest, only a few days, whereas, introducing single donation NAT will fairly dramatically further reduce the HBV window and therefore the resulting theoretical residual risk.

[Slide.]

In this cost effectiveness analysis, we put in some sort of assumed or projected costs for minipool HCV and HIV, which is currently in place in the whole blood sector. Post-licensure, we predict that the cost will probably be in the range of $12 per donation. That is as applied to pools in the 16 to 24 range. This is a per-donation cost. We looked at ranges of 8 to 15.

Going to single donation NAT, we assumed that would be on an automated platform which would reduce labor costs, and this would then be each donation tested

individually. We assume in this model a $15 per donation.

Then, for the purpose of this discussion, we assumed that adding HBV to these platforms would be relatively less costly because it is simply adding another marker to a probably multiplex type assay, so in this model we assumed a $3 increment of minipool or single donation to add HBV with a $2 to $4 range.

[Slide.]

Now, very important is what is the relative implications of preventing or transmitting HIV versus HCV versus HBV. This factors in obviously the probability that a person who is exposed to a viremic donation will become infected, persistently infected, and will then evidence disease and require therapy downstream.

It is really the relative numbers here, which I think are very striking and very important to today's discussion. This is the number of quality-adjusted life years saved per infection prevented in the context of a transfusion analysis. This again is data from Jim AuBuchon's group.

You can see that for HIV, preventing 1 HIV infection will save 7.1 quality-adjusted life years. This is in the context of the usual transfusion recipient, you know, a 50- to 60-year old person surviving underlying disease to live a year, maybe half the time, et cetera.

In contrast, HCV, because most of these infections, although they become chronic, are asymptomatic for decades, there is about a 10-fold lower benefit to preventing those infections or 10-fold lower clinical consequence of transmitting NAT infection.

Then, for HBV, it is even less, 0.1, so it is 1/70th essentially of the importance of preventing HIV from a cost effectiveness perspective, and that is again because most HBV transmissions are subclinical transient infections that resolve completely, and of those who become chronic carriers, a relatively small proportion will progress to clinical disease.

[Slide.]

So, when we translate that out in terms of QALY saved by minipool versus individual donation NAT by virus, you can see that for minipool NAT, most of the benefit is coming for HCV because of the very long plateau phase and the very large number of HCV infections prevented.

The benefit for HBV is really extremely low because, one, there are very few infections detected by minipool that are not detectable by surface antigen based on the model, and, two, is the clinical consequences are fairly modest.

Single donation NAT interestingly, even though we are only predicting to prevent 3 or 4 additional HCV or HBV

infections, the benefit on a quality basis is larger because these are more important whereas, for HBV, will prevent about 30 with single donation, but again the clinical consequence, and therefore the cost effectiveness benefit, is small, 7.

[Slide.]

This just summarizes all of this in terms of quality saved, so minipool NAT would be predicted to save 71 quality-adjusted life years, and moving from minipool to single donation NAT would be predicted to only save an additional 8 quality-adjusted life years even though you will prevent a large number of HBV transmissions.

[Slide.]

Finally, the sort of bottom line of these assays again, not particularly relevant to this committee's charter and discussion, but the cost effectiveness of these various interventions, either minipool NAT for HIV, HCV, as currently performed, based on this analysis, the number comes out at $3.2 million per quality-adjusted life year. On the baseline analysis and depending on the cost range, could range from 2.2 to 4 million per quality-adjusted life year.

Interestingly, in this analysis, going to individual donation, combe testing for HIV and HCV actually is slightly more cost effective, still extraordinarily high

cost per quality on a public health basis, 2.7 million per quality life year.

Relevant to this discussion, adding HBV to either of these strategies worsens the cost effectiveness output it actually takes for the minipool goes from 3.2 to 3.8 million per QALY and for the individual, from 2.7 to 3.0 million per QALY.

This other column actually shows how much these tests would have to cost in order to reduce the dollars per QALY to the generally accepted non-transfusion medicine public health threshold of $50,000. The bottom line is these tests would have to cost about a quarter per donation in order to get us into the same ballpark as other public health measures are currently being implemented.

[Slide.]

Finally, the last slide just to acknowledge the large number of people who really contributed to this specific area of work. Lorraine Peddada and Chuck Heldebrant have done an enormous amount of work characterizing these panels and collaborating to contribute data and analyze the data.

Rich Smith and Andy Conrad at NGI generated all the viral load data. Steve Raid, BioClinical Partners, they manage the compilation of these panels. David Wright, George Schreiber, and Steve Kleinman, very active in the

analysis, particularly David who developed and has done a lot of work to derive models appropriate to the data analysis.

Eberhard Fiebig, who works with me at UCSF, in terms of the modeling, and then Brian Jackson and Jim AuBuchon who did the cost effectiveness analysis.

Thank you.

DR. NELSON: Thanks for a very nice comprehensive analysis.

Are there any questions or comments by the committee, or anybody?

DR. CHAMBERLAND: Mike, that was very nice. I have one question. Before you led into all of the analyses that gave us the QALY information, there was a slide in which you compared the calculated risk of viral infection per million red cell units tranfused, and for HBV, the baseline risk was 5.5, and then you showed there would be a modest decrease with implementation of minipool NAT and even more with single donor.

Is that baseline risk of 5.5, that is obviously using current antigen tests, and my understanding I guess what we are going to be talking about is that on the horizon, there are other antigen tests that are even more sensitive, so in point of fact, if those antigen tests were to be available, then, these analyses might actually change?

DR. BUSCH: Right. This number of 5.5 per million is closer to about 1 in 150,000, 1 in 200,000, which is quite a bit lower than the original REDDS estimate in the Schreiber paper, which was like 1 in 60,000. That is in part because we have now documented a reduction in HBV incidence.

Also, in this analysis, we did already factor down that the antigen tests seemed to be more sensitive than were the basis for the original window period estimate because this analysis used the data from the study I just presented, assuming that we had an antigen test with a 3,000 genome equivalent sensitivity.

Now, actually, you will see data later from Dr. Biswas that does show that the more sensitive antigen tests will further reduce that close to the level of what minipool NAT could achieve, but not quite there.

DR. NELSON: I think one other issue is that this analysis applies to the current like donor population in the U.S. If the characteristics of the donor population were to change, there are subgroups that would not be excluded necessarily on the basis of drug use, et cetera, that still have higher HBV incidence, and so that this could change some of the calculations.

It is maybe not likely that there will be dramatic changes, but certainly, you know, in the context of Japan, I

would think that NAT testing would be far more cost effective and useful, particularly in the absence of core, which they can't do because of the very high prevalence of core, but nonetheless, even in the United States, if there were some substantial changes or even maybe modest changes in the donor population, these figures might change.

DR. BUSCH: Right. In the REDDS group, we have done extensive analysis that demographic correlates have incidence and prevalence for each virus, and obviously, HBV particularly the incidence is clustered in younger donors and certain racial ethnic groups, et cetera.

The other thing that is evident, in I think some of the comparisons Dr. Tabor alluded to, the yield of HBV NAT in the U.S. plasma donor sector--and there again there is probably an underlying difference in the incidence rate, which explains that differing yield.

DR. NELSON: Other comments?

DR. KOFF: Dr. Busch, with regard to your comments about the relative benignness of hepatitis C, I think it is less clear that it is that benign in the population you are talking about of transfused people. In other words, all or most of our data on the natural history of that infection long term has come from looking at relatively young people except for the transfusion studies done in the 1970s.

There is a sense that the disease is, in fact,

less benign, more rapidly progressive if you are a bit older when you acquire this infection, so that may be something that needs to be looked at in terms of the impact of additional testing.

DR. BUSCH: Yes, although I do think that particularly Leonard Seefe's long-term compiled follow up of posttransfusion HCV cases continues to show that only I believe 10 to 15 percent after two or three decades have progressed to clinically significant liver disease. So, those are the numbers that actually were used in this model.

DR. KOFF: Yes, you are right in that, of those folks who he has now followed up to 25 years, those who are selected and have been biopsied, of course, about 30 percent have cirrhosis, so they are now in a different track in terms of survival.

The younger folks that have been looked at, the Irish women's study, for example, and the Air Force recruits seem to have done considerably better.

DR. BUSCH: Right.

DR. NELSON: Yes.

DR. MACIK: I have one question, that is a major difference between the hepatitis B and hepatitis C or HIV, is that there is a vaccine. In talking about all of this, where is the cost estimate of screening for people who have been vaccinated?

The point was made if the donation pool characteristics were to change, well, we have a whole generation that have been vaccinated against hepatitis B, how likely are they to fail the vaccination, i.e., get hepatitis despite being vaccinated, when that pool reaches blood donation age, how is that going to change all of these characteristics, and should more effort be being placed on getting everybody vaccinated, unless there is a major problem with the vaccination process, i.e., it causes a second disease or it is ineffective or wears off in five years, none of which has been really shown?

So, I wonder, you know, if you really factor in that, what cost difference are you making, because we are looking, you know, at more and more for testing when we have a potentially totally preventable disease here.

Have any of the studies or has anyone looked at where vaccination would impact on screening for hepatitis B?

DR. BUSCH: Of course, the vaccine induces antisurface, and we don't screen for that, so it is not going to be a problem in terms of inappropriately losing the vaccine donors.

All it could do would be to make the projected yield lower because your underlying incidence will decline of true HBV infection on top of vaccine, which will then translate into a poorer cost effectiveness analysis output,

so it could just make matters worse from a benefit perspective.

DR. EPSTEIN: Mike, could I just trouble you to reconcile numbers on two of your slides on the health benefit, could you go back and show the quality-adjusted life years saved for the individual agents and then compare that to the sum that you had, because it would appear that there is a large discrepancy if you look at minipool NAT, and then that has a major implication about the additive value of single donor NAT.

DR. BUSCH: Right, if we can get back to the slides. Again, these numbers are coming from Jim and Brian Jackson, who works with Jim, so I can't defend them in great detail. These newer numbers, which aren't included in the handout, but were in the slide I just requested from them because I think they are so important to clarify.

Just page on through to probably close to the last slide, but importantly, one issue, there, I think this is what you are alluding to.

DR. EPSTEIN: If you take those figures and you multiply by numbers, on a subsequent slide, now, if you were to add across the row, just for argument's sake, take minipool NAT--

DR. BUSCH: This represents the benefit of minipool NAT, independently then looking at the benefit of

single donation NAT, whereas, the other slide was the incremental yield.

DR. EPSTEIN: Right, I understand that, but just take minipool NAT, okay, if you add across, right, you get about 50.

DR. BUSCH: Right.

DR. EPSTEIN: But if you go to the slide where you looked at the sum of quality-adjusted life years, you have got 71.

DR. BUSCH: Go to the next slide.

DR. EPSTEIN: 71. Let's look at the right. Now, look at minipool NAT. Now, 71 and 50 are way off, and that then drives the estimate for the additive value of SD-NAT, as 8 would become 28.

DR. BUSCH: I can't give you the full clarification on this, but one of the caveats that was presented with this slide is that this analysis, as the footnote indicates, factored in that a patient had to survive at least one year in order to achieve any clinical event as a result of the infection, and therefore, only contributed. I can't explain why you would have a greater number.

Again, I can't defend the details on all of this. I think perhaps the most important message here, given that this doesn't per se deal with cost issues, is that concept

of the relative clinical importance of prevention of HBV versus HCV and HIV.

DR. NELSON: Any more?

Next, Susan Stramer from the American Red Cross.

Susan Stramer, Ph.D.

DR. STRAMER: I am also going to present, prior to Dr. Biswas' presentation of the FDA comparative studies, comparative studies that were performed at the Red Cross.

[Slide.]

Some of these studies were shown last year, so I guess this celebrates a one-year anniversary, and additional studies that I have done for some evaluations the Red Cross has been performing.

[Slide.]

The objective for both BPAC meetings, that is, last year and this year, is to compare the sensitivity of current HBsAg and newer generation HBsAg assays, including those that are licensed and unlicensed, to NAT, and what we used for our NAT was the National Genetics Institute PCR test as previously described by Mike. Again, we tested seroconversion panels looking at front-end detection, that is, pre-HBsAg positives.

We tested individual units and then extrapolated cutoffs that would be achieved by pooled NAT tests.

[Slide.]

From the first studies that we had done, we looked at 13 plasma donor panels with the NGI test, totaling 181 samples. What you have here is a box and whisker plot showing the viral loads at various stages of HBV seroconversion. The horizontal lines show you theoretical cutoffs. This first one for NGI is what the source plasma industry was using at about 6,000 copies per mL, which is now lower.

This represents, instead of using--and I will show data using 1,000 copy cutoff for pooled NAT--I am showing in most of my slides 1,600 copies per mL as the cutoff for pooled NAT as that is really our working cutoff currently for HIV and HCV in that we use a test for HIV and HCV that have 100 copy per mL sensitivity 95 percent of the time, and the smallest pool size used is 1,600. So, for the sake of these comparisons, we are using 1,600.

What you see here are the viral loads for the DNA-positive samples, that is, the HBsAg negative. This is the viral load at the HBsAg positives using the current Abbott 75-minute test that many blood centers use, and then this is later after the development of antibody.

But if we focus just on the DNA positives, we see that the median or the 50 percent mark of the population is that 600 copies per mL, well below the cutoff achieved at 1,600. There are 5 samples that would be detected of the 13

donors, that would be detected above the 1,600 per mL cutoff.

[Slide.]

You should have this in your handout. This represents the raw data from the study, and I won't go over it in detail.

[Slide.]

Just to look at some of the representative seroconversion panels as markers develop after HBV infection. In orange we have HBsAg, in pink we have HBV DNA. You can see clearly that the two parallel. The horizontal lines here again represent the same cutoffs as described, and the blue and green lines demonstrate the production of antibody.

What you have here by the "fatter," if you will, symbols, is the first positive by DNA and then the first positive by HBsAg. There is one sample here that would not be detected by pooled NAT, was HBsAg negative, and you can see, as Mike demonstrated, that these early samples have relatively low viral loads, this one again about 600 copies per mL.

[Slide.]

Here is another such panel where you can see the HBsAg increase and the DNA increase parallel. In this case, there are three samples that represent kind of a shoulder of

samples that would not be detected by minipool NAT at a 1,600. They may be right at the cutoff if one were using 1,000, and they are HBsAg negative by the current licensed test that was used in the study.

[Slide.]

Following this study, we also did a comparison of two licensed HBsAg assays, again to show the variability. What we focused on in the first study was NAT versus one licensed assay. Here are two different licensed assays just to show you the variability.

Here, we used 21 seroconversion panels, Genetic Systems, the Shaker procedure. They have two licensed protocols in their assay. The Shaker is more sensitive, and the Ortho procedure used by many blood centers.

Of 184 samples in this evaluation, there were 57 that were negative by Ortho, but positive by the Genetic Systems Shaker assay. Of those 57, 56 were DNA positive. The analytical sensitivity, to give you another calibrator or another idea of sensitivity of these assays, if you look at purified HBsAg standards, you can derive analytical sensitivity, and the analytical sensitivity in this study for Genetic Systems was about 0.14 to 0.34 for AD and AY, and for Ortho it was at 0.8 or greater.

[Slide.]

Another evaluation that we participated in are the

Abbott clinical trials for Prism, involved 25 HBsAg seroconversion panels. Here, you can see a more theoretical graph showing HBsAg EIA detection by their current test, but the Prism test would buy you both in back end, which I can't see the number clearly, but I believe is 12.8 days in back end when anticore becomes positive, and 6.8 days front end closure when DNA copies are still fairly high.

Moving into the DNA positive period prior to HBsAg becoming positive by Prism, you have lower viral loads. These analyses were done only in a subset of the panel, but again these viral loads would not be predicted to be detected by pooled NAT.

[Slide.]

So, if you kind of take the spectrum of what we know about licensed and unlicensed tests for HBsAg, we have ranges in sensitivity that range from 0.08 nanograms per mL to greater than 0.7 nanograms per mL. What the industry uses today for screening really is in this spectrum.

As I mentioned, there are two protocols licensed for Genetic Systems, and they do represent even a range within a one-licensed assay reagent. The same thing is true for Abbott. This is an overnight procedure versus a 75-minute procedure, but here we can see the more sensitive assays, the overnight Abbott, Genetics System Shakers I just showed you. Ortho has a test before FDA that has about a

0.1 nanogram per mL sensitivity, and then the Abbott Prism that runs about 0.8 to 0.9 nanograms per mL.

[Slide.]

We have now done a subsequent study to investigate the variability in HBsAg assay sensitivity, and again to compare that to pooled NAT and individual donation NAT. This study involved 17 commercial seroconversion panels sourced from Bioclinical Partners. The assays involved were really the spectrum of panels of assays that I just showed you, with Abbott Prism being the most sensitive.

In contrast to what Mike showed, this comparison was done using the U.S. protocol, which has a decreased cutoff relative to the European protocol, so it would be more sensitive than what Mike just showed.

We used Auszyme Procedure C, the Abbott current, the Ortho current, both 75 minute procedures, and Genetic Systems Static, which is the less sensitive of the two protocols from Genetic Systems. We didn't run this, but data were provided by the vendor.

There were a total of 225 samples. For PCR, we ran an Ultra-Qualitative test from NGI, and UltraQual-positive samples were then quantitated by their SuperQuant assay. The Qualitative test has great sensitivity at 4 copies per mL than Quant at 100 copies per mL, so what we did was if we had a qualitative PCR-positive sample that was

Quant-negative, we assigned it a value of 50 copies per mL for the analysis.

Of the samples tested, 156 or 69 percent were DNA positive individually.

[Slide.]

The cutoffs used for Quant PCR to extrapolate to the use of pooled NAT were 1,600 for the reasons I explained before, 1,000 to compare with the study that Mike presented, and then we used a 320-copy per mL cutoff, which is really a low cutoff for pooled NAT to represent 95 percent detection if we were to use assays that had 20 copy per mL sensitivity.

[Slide.]

The next three graphs show you a comparison of three HBsAg tests, the Ortho current, the Abbott current, and Prism. There were 156 DNA positive samples. The Ortho current test detected 31 percent of them. If you plot DNA viral load against HBsAg, this is the distribution of points you have. We have a cutoff of 1,600 and a cutoff of 1 for the HBsAg test. So, the important cell to focus on is this first cell, because it represents those that would be picked up by pooled NAT, but that would not be detected by HBsAg.

So, with the Ortho test here, where 31 percent of the samples were HBsAg positive of DNA positive samples, we have 36 here that would benefit by a pooled NAT test.

[Slide.]

This is now the Abbott current procedure where we now have 41 percent of the DNA positive samples HBsAg positive, but instead of having in the previous slide 38, I believe, samples that were not detected, here, we only have 21 samples that were not detected by pooled NAT.

[Slide.]

In comparison to Prism, what we find now is you can see more of the distribution of HBsAg S to CO move to the right or to higher S to CO values, and the number here going from 38 to 21 now is at 5, so what we have using a cutoff of 1,600 is 5 samples that would be pooled NAT-reactive HBsAg negative.

Interestingly enough, in the other plots I showed you, we only had 1 sample in this box for the Ortho and for the Abbott other assay, and this box here represents HBsAg-reactive samples that would be negative by pooled NAT. So, interestingly enough here, if you are doing a comparison, you have a tradeoff and that here you have 6 HBsAg positive samples that would not be detected by pooled NAT, whereas, here you have 5 samples that would be detected by pooled NAT, but not HBsAg.

[Slide.]

To look at different cutoffs or what is the effect of dropping the cutoff for pooled NAT, looking at these

samples, from 1,600 to 1,000 to 320, if you change the cutoff for pooled NAT to 1,000, of those by Prism that were HBsAg negative, you would have no further increase. You would actually pick up one more by pooled NAT of those that I showed you that was already HBsAg positive. With the other assays you would add 1 HBsAg negative sample.

Now, moving the cutoff to 320, however, does have a more significant impact, as one would imagine. There were 9 samples that were detected by pooled NAT that weren't detected by Prism and 12 samples for the other assays.

[Slide.]

If you look at all of the assays evaluated in this study and look the viral loads at the time of first detection, that is what this graph shows you against viral load. These are box and whisker plots, these are the medians, and the assays are labeled down here on the x axis with the time at which the assays became positive.

So, here you have the three assays at the extreme, here you have the Prism viral loads, but what you see here, looking at the first PCR positive and the last PCR positive is a 21-day window in which viral loads are relatively low. In fact, the mean of the last PCR positives, the median is well below the cutoff of 1,600, and 75 percent of the samples are represented in this range.

[Slide.]

To look at these values numerically, here is the median copy level and the min and max, and again for the days. So, Prism then became positive at day 27 followed by the other assays at later times, but it is interesting to note the viral loads, the increasing viral loads that correspond to HBsAg detection.

[Slide.]

Doing the same type of analysis, as Mike did, to ask the question, but using a less sophisticated model, what is the corresponding copy per mL at the cutoff of each of these assays. What I showed you previously is what the assays detected using the bias of time in the panels, but if we eliminate time and just say what is detection at the assay cutoff, we did this by looking at the first positive bleed per the assay and the last negative, and doing a linear regression, but in order to make that more robust, we compared that then to looking at the last two negative bleeds and the first two positives or including three negatives and three positives.

Well, for Prism, you really don't get much of a difference, and you get about 1,500 or 1,400 copies per mL of HBV DNA that corresponds to detection in the Prism assay. You get about 5,700 using the current Abbott procedure, and anywhere from 18,000 to 8,100, there is a little bit more variation in the least sensitive assay.

[Slide.]

So, as far as summary and conclusions, we did see that significant differences in sensitivity exist between different HBsAg assays. The detection of purified HBsAg ranges from greater than 0.7 to 0.08 nanograms per mL, so that there is almost a log difference.

This difference translates to a mean of 17 1/2 days or 2 HBsAg positives detected per million tested, and this was using ARC 1998 to 1999 incidence rates of 4.5 per 100,000. In the previous study that Mike showed, the REDDS numbers of a similar time period are similar there at 5.1 per 100,000.

HBV DNA can be detected for a mean of 21 days prior to the appearance of HBsAg even using the most sensitive HBsAg tests.

The median HBV DNA titers in HBsAg negative samples, again by the most sensitive assay, were a median of 100 to 500 copies per mL with 75 percent being less than 2,000.

[Slide.]

Prism detection corresponded to HBV DNA of approximately 1,400 copies per mL versus 5,700 or 18,000 for currently used HBsAg assays.

The current HIV and HCV NAT cutoff that we used for a 95 percent detection is 1,600 copies per mL, so you

can see how these two compare.

Pooled NAT using a cutoff of 1600 copies per mL would detect 5 additional DNA positive samples of 156 DNA positives in the 17 HBV series I showed, but failed to detect 6 that were reactive by Prism.

Dropping the NAT cutoff to 1,000 copies only added the detection of 1 sample, and that 1 sample was already HBsAg positive. Dropping the cutoff to 320 improves the yield by 9 HBsAg negative samples or 13 total samples.

The use of a more sensitive HBsAg assay appears to be equivalent to the performance of pooled NAT using a cutoff of 1,000 to 1,600 copies per mL.

Thank you.

DR. NELSON: Thank you, Dr. Stramer.

Any questions or comments? Yes.

DR. SIMON: Dr. Busch alluded to this, and I didn't ask it then, but might ask it now. We have this period of low levels of HBV virus that can be detected by nucleic acid testing before any of the assays.

What is the infectivity during that period, what is known about the infectivity during this period, that is, to what extent can we say whether the units would be infective or not?

DR. STRAMER: One of the bullets that Mike had for his subsequent work that he didn't have, and I have

italicized as done, were studies such as that to do chimpanzee infectivity studies looking at what represents infectivity in these early samples.

We certainly know for HBV from health care workers that the infectious dose corresponds to a low viral load, I can't remember in terms of Danes what it corresponds to, but certainly HBV represents a very infectious agent.

So, my guess is on the 21 days of samples I showed you, that those certainly, especially in the absence of antibody, would represent infectivity.

DR. SIMON: So, you believe all the ones you are detecting by nucleic acid testing are probably infectious.

DR. STRAMER: That would be my guess, and we are talking about a number of copies per mL, if you consider what a unit of red cells is, that would be a far greater amount of inoculum.

DR. NELSON: Other questions or comments?

DR. FITZPATRICK: On the comparison of PCR to the Abbott Procedure C, the samples that were in the lower quadrant there, that were HBsAg C positive and PCR negative, I can't read that--is that 6?

DR. STRAMER: For Prism, it was 6, yes.

DR. FITZPATRICK: What about for the--

DR. STRAMER: The other two, they were 1.

DR. FITZPATRICK: They were 1? Okay.

DR. STRAMER: Yes.

DR. FITZPATRICK: Were they the same ones?

DR. STRAMER: Yes, the same one, and then five additional for Prism, correct.

DR. FITZPATRICK: Any speculation on how Prism is picking up?

DR. STRAMER: Well, I mean we don't live in a totally linear world, so there are, you know, exceptions where I mean we are giving means, but certainly confidence intervals around those means are going to be large, so it is just variation.

DR. FITZPATRICK: I was just curious as to why you used the non-Shaker method for Genetic Systems.

DR. STRAMER: We actually didn't use it. Interestingly enough, even though there are two procedures that are licensed with that set of Genetic Systems' reagents, most of the industry who uses Genetic Systems chooses, as least in the U.S., Canada uses the Shaker procedure, just to give you a contrast, but in the U.S., they use the Static procedure.

We didn't actually run that. Those data were provided by the vendor. So, the source plasma company who found those panels, that is their test of record, so we were able to gather those data from Bioclinical Partners.

DR. FITZPATRICK: Thank you.

DR. NELSON: Jay.

DR. EPSTEIN: Susan, you showed us that if the minipool NAT were performed at a sensitivity of 320 gEq/mL, that really there was a dramatic additive benefit compared even to the newest HBsAg assays, so the question is really what is the feasibility of achieving that level that would not appear to be the level of the current systems, so can we get there.

DR. STRAMER: I can't answer that question. I mean technically, I would think certainly we could get there, but, you know, there are other hurdles to implementing minipool NAT in addition to sensitivity. If we assume all other things are negated, that is, CGMP or process control or the IND, the regulatory issues, the validations, et cetera, if we look purely based on sensitivity, of course, this would be something I believe that we could achieve.

We didn't think that we could achieve NAT testing for HIV and HCV, the way we have it in place now, and it can be achieved. I mean I think we have seen data from Roche, as an example, to suggest that their HBV DNA tests can achieve 20 copies per mL, but I don't know in the wider experience how that will translate.

DR. NELSON: Dr. Busch.

DR. BUSCH: Susan, those five or six samples that

you detected as Prism antigen positive, but projected would fall below a minipool NAT detection limit, just a little caution on those. You are relying on the primer specificity and quantitative capacity of the NGI assay in inferring that those would be negative by a pooled NAT.

It is critical that we understand whether indeed if we were to introduce pooled or even individual donation HBV NAT, whether there would be any residual benefit to surface antigen detection, particularly in the front end.

So, I would suggest that the value of actually running those specific samples on dilutions relevant to the current prototype or existing HBV NAT testing, wouldn't be surprised to see if those actually could be detected at dilutions with these, you know, more robust primer qualitative tests that wouldn't correlate with the titer, the concentration from their quantitative assay.

DR. STRAMER: Certainly, that is true. I think we would see variability, the same ways we have seen variability with other tests by running pooled assays. Again, these were extrapolated cutoffs, and these weren't actually, as the FDA study will show, actually running the samples in their minipool dilutions.

DR. NELSON: Any other comments? Thank you.

The next speaker is Dr. Robin Biswas from the FDA.

Robin Biswas, M.D., DETTD, OBRR

DR. BISWAS: Good morning.

[Slide.]

At the March BPAC a year ago, the Red Cross suggested that HBV NAT testing of source plasma donations using the 512 sample pool testing format might not be much more sensitive than testing single samples by current HBsAg assays, and, in fact, might possibly be less sensitive than testing single samples by newer, more sensitive HBsAg assays.

[Slide.]

So, our response was to design and perform a study with the NAT Study Group, and the sort of over-arching idea was to compare HBV NAT with HBsAg testing, particularly with the more sensitive tests, and the second thing that we wanted to do was to compare the current HBsAg assays with newer HBsAg assays that are under development, and this was going to be done using seroconversion panel samples from cases of acute hepatitis B virus infection.

[Slide.]

You have already seen this slide. The NAT Study Group is composed of liaisons from government agencies, blood organizations, and industry, from some of the assay manufacturers, the NAT assay manufacturers.

[Slide.]

The specific aim of the study was to estimate the

increase in yield of detecting a greater number of HBV infectious units comparing the current HBsAg assays, the newer, more sensitive HBsAg assays, the NAT pool testing methods, and the NAT single sample and NAT single sample testing.

Now, going back to the NAT pooling test methods, I just want to briefly say that there are two pooling methodologies involved here. One is the source plasma method where they use large pools of 512 or, another manufacturer, 1,200 pools, thereby diluting each sample in effect, each individual sample is diluted 1 to 512, and 1 to 1,200.

The other format is the testing for whole blood, which is used, actually not for HBV NAT, but for the HIV and HCV whole blood NATs, and the pooled samples there are much smaller. The pooled samples are 16 from some manufacturers and 24 with others. So, the dilution of the individual samples that are being tested is lower, the dilution is lower.

[Slide.]

We selected 10 seroconversion panels from a total of 23 that had been collected by Impath and Bioclinical Partners, and these were from source plasma donors. They are serial bleeds from source plasma donors who seroconverted to HBsAg positivity in the acute phase.

The panels had been previously tested in a variety of HBsAg tests and also in one HBV nucleic acid test, and this had been done at various locations, and it really wasn't quite clear whether these tests were--some of them were certainly not licensed in the U.S., and so there were some unknowns about that. But I should say that the testing results that had been previously done did help us to select the 10 seroconversion panels.

[Slide.]

Ten samples from each of the 10 selected seroconversion panels were chosen for both hepatitis B surface antigen and HBV nucleic acid testing equals 100 samples, and all these samples were coded.

The samples were chosen on the basis of being in the viral pre-ramp-up phase, that is, that phase that Mike described earlier, it's a smoldering low viral load time, and as Susan said, probably infectious, followed by a viral ramp-up phase, the two or three days viral ramp-up phase.

We also included 28 samples that were controls.

[Slide.]

The controls, each control was provided in duplicate to the testing labs under code. The controls consisted of the CBER HBsAg lot release panel with 8 positive samples and 2 negatives. These 8 positives, we know what the HBsAg concentration is in those 8 positive

controls, and they go from an estimated value of about 0.02 to about 7.5 nanograms.

There was a sample of normal human plasma. Remember, this was all in duplicate and coded.

Third, we used dilutions of the WHO HBV DNA NAT standard at dilutions of 4,000, 400, and 40 International Units per mL.

[Slide.]

Now, all 128 samples were coded and tested. We tested them in 7 different HBsAg procedures in our lot release lab. HBV NAT testing was done by actually four representative manufacturers, and they used also the source plasma format that are described in the whole blood format with those different pool sizes and hence different dilutions for the individual samples, and also, three manufacturers tested in a single sample format.

[Slide.]

Now, the methods of analysis. Mike Busch's group and the group at Westat compared rates of viral detection in the pre-ramp-up phase and ramp-up phase specimens. We estimated differences in the viral load at cutoff, using a longitudinal regression method--I am sorry, that is not quite right. I think Mike's group used estimated differences in viral load at cutoff, using a longitudinal bivariate regression method that he talked about earlier.

We estimated differences in viral load at cutoff for the different HBsAg assays using the WHO HBV standard. We also estimated the HBsAg concentration in nanograms per mL at the cutoff using our lot release panel of known concentration.

Mike's group and the group at Westat, they compared window period differences both for the NAT assays and for the HBsAg assays. They used two different methods for the HBsAg assays.

[Slide.]

Most important, we project the yield, the increase of yield meaning how many more units are you going to pick up compared to what the current tests are doing, and that was based on the window period and known HBV incidence.

[Slide.]

Now, there were limitations to this study. There was a limited data set of 10 samples from each of 10 seroconversion panels. The donor was sometimes positive on the first bleed, so you couldn't do really a window period difference analysis.

There was a limited ability to perform replicate testing because of limited volume, and the HBsAg analysis was based solely on initially reactive results, so there were some weaknesses in it. Nevertheless, we got some very interesting results.

[Slide.]

Now, what is all this about? This is a plot of five members of the lot release panel containing known HBsAg concentration in nanograms against the sample to cutoff ratios that were obtained when we actually did the testing. So, this is 1 nanogram, this is 0.9 nanograms, this is 0.5 nanograms, and down here we have 0.04 and 0.02 nanograms. Then, to estimate the HBsAg concentration at cutoff, there is the sample to cutoff ratio at 1, at cutoff, go across here to the y axis, and you get a result of 0.18 nanograms per mL for this particular assay. We coded all these assays.

[Slide.]

Using those curves that I just showed you, we estimated the HBsAg nanogram at cutoff for all these different tests, and what you see here is a comparison of the seven procedures.

I have coded it, and I should say that it was very important to the manufacturers that we did code everything, otherwise, they wouldn't have taken part in the study. But just going through this, these results you will see sort of replicate themselves sort of in many of these studies.

A and B sort of are down here, and F and G are sort of up here, not so, you know, they don't pick up as well as these, and D, E, and C sort of change around a bit.

I should say that these are unlicensed, this is a licensed, this is unlicensed, these are all licensed procedures.

[Slide.]

This is the estimated viral load at cutoff of the different HBsAg tests. This was done by plotting the sample to cutoff ratio against the WHO dilutions, and these are International Units per mL at the cutoff. We use a conversion factor of 2.5, I believe, and here again you can see that the order of sensitivity, if you will, is sort of very similar to the nanogram concentration at cutoff.

[Slide.]

We are coming now to Mike Busch and the Westat data. This is a comparison of HBsAg assays for detection of pre-ramp-up and ramp-up samples. This column here, well, here are the coded HBsAg procedures. This row here just shows the number of actual samples in the ramp-up phase that were detected, and you can see it is just 1, you know, sort of just 10 percent, well, just 1 out of the 10.

This is the number of samples that were detected in that ramp-up phase in the two-three day time period, and out of a total of 90, I think for this it is a little bit different because--but, anyway, what you can see is, is that there is an order here again. It actually goes through the alphabet here, from most pickup to least pickup of these HBsAg assays.

What we have here is the viral load at sample to cutoff ratio. This was done by Mike Busch and the Westat group. It is very, very slightly different to ours, and it is different in sensitivity, compared to this here.

What you see is that the viral load for the procedure A is at 568 at cutoff, viral load is 568, and here at G, it is 10,000 about.

[Slide.]

This is an illustration of the last column of the previous slide. Here you can see we have put in the confidence, the variation of confidence intervals here. Of course, they do overlap quite a bit, but nevertheless, you can see that there is a difference between sample to cutoff ratio at 1 cutoff, between the licensed tests and the unlicensed tests. Note that this one here is actually, this licensed one is actually quite getting to be similar to the unlicensed sensitive assays.

[Slide.]

I am not going to dwell on this one. It is this longitudinal bivariate analysis done by Michael Busch. What is important to note is that using this, you can get the window period differences, and the window periods have been estimated from the doubling time and the viral load at cutoff model.

What is important to realize is that this window

period between the most and the least sensitive HBsAg assays, here at 11.45 days, the important point here is that it is a quantitative estimation, if you just keep that word "quantitative" estimation, done by the doubling time, this again shows the most and least differences at serum to cutoff ratio, at cutoff, and this is the 10,000 cutoff assay. It is assay G, I think, and this is the cutoff by assay A.

[Slide.]

Now, this analysis here, the window period reduction by days, by the newer HBsAg assay as compared to the current licensed assays, and what you need to know here is that this is a qualitative way of estimating window period differences.

What it is saying is was the sample positive or negative, when did the sample become positive in one test compared to another test. A positive value here, this window period difference here in this row here, a positive value represents window period reductions by the new unlicensed assays versus the licensed assays.

What you see here is that this unlicensed A precedes by 12.2 days to D detecting a test, and here it is 15 days. This is picking it up earlier by 15 days, and this one here isn't picking it up as early.

We put in the standard errors, and, well, they are

kind of large, but it does show you basically that the unlicensed assays do pick up--some of the unlicensed assays do pick up quite a few days earlier than the licensed assays.

[Slide.]

This is a comparison of the NAT assay detection of the pre-ramp-up and ramp-up HBV viremia. Just note that, on the whole, the single unit--I should say that these are the three manufacturers that tested, used their test on a single unit sample--and note that single unit, on the whole, is higher than when you do plasma testing. I will come back to this.

It is the same sort of idea here. The number of ramp-up units that is picked up by the single unit as compared by the pool testing is much larger.

Now, this is very interesting data. As I said, the plasma pool testing, the pools are much larger. They are either 512 or 1,200, and these pools are much smaller, so you would think that this would pick up more than that, but particularly here, this is picking up this one here, this test here is picking up a lot more--well, I guess the numbers are small--but it is picking up more units than this one, and this one isn't picking up any, despite the fact that these two are smaller, they are more diluted than this here. You see something similar here, as well.

[Slide.]

This analysis is the window period reduction in days by the NAT assays compared to HBsAg assays. The best way to look at this is--I wish I had time to do this, to put in a thick line here and a thick line here--if we go across A and B, if you compare A and B, which are unlicensed sensitive tests, if you compare that with the single unit NAT, these numbers are positive, so that means that the single unit NAT is picking up quite a few days before even the more sensitive tests.

When you go down here, it is quite clear that the single unit NAT is picking up samples about a month before the currently licensed tests. These are currently licensed tests.

Now, when you move over to here and look at the pooled NAT, what you see here is really very, very interesting. You see here that in the plasma format, here is a negative number, one of the whole blood formats is definitely a negative number.

This is really saying that this test is picking up, this HBsAg assay is picking up before the pooled NAT assays. This slide also shows that the whole blood assay is sort of less sensitive or picks up later than the larger plasma pools.

What I would say is that here, well, this seems to

show that sort of pooled NAT is sort of on par with the more sensitive assays under development, and this quadrant here seems to show that pooled NAT is picking up some more, is an improvement compared to the currently licensed assays.

[Slide.]

Now, this is the relationship between HBV window period differences and the actual yield of HBV-infected whole blood donations, and it is based on the REDDS HBV incidence rate, which is at 5.1 per 100,000 persons a year, and so what this means is that with the window period difference of 1, you get a yield over and above current tests of 1.4 donations per 10 million, and the window period difference in days of 30, you get a yield of 42 units over current testing.

[Slide.]

Now, what is the benefit of the new HBV detection methods? Well, using the previous table, the window period reduction in days compared to current assays, if you use the new HBsAg tests, you get a window period reduction of between 11 to 15 days, with a yield of 15 to 21 donations per 10 million.

Pooled NAT would bring you a window period reduction of 9 to 11 days, with a yield of about 13 to 15 donations per 10 million, and the single unit NAT would give you a window of 25 to 36 days, and a yield of 35 to 50

donations per 10 million.

[Slide.]

So, the conclusions are that this empirical study sort of agrees with the previous modeling studies that have been described. There are definitely differences in sensitivity between licensed and some of the newer unlicensed HBsAg assays.

These differences appear to correlate with estimated viral burden at cutoff and to translate into a diminished window period of 11 to 15 days, which would give you an increased yield of 18 units, about 18 units per 10^7 donations.

[Slide.]

The sensitivity of the newer HBsAg assays is comparable to pooled HBV NAT.

Single unit HBV NAT reduces the window period by about 20 days compared to the newer HBsAg assays and pooled HBV NAT assays, and that translates into an increased yield of about 15 units per 10 million.

Lastly, the 25 to 36 days compared to the current HBsAg assays with an increased yield of 42 units per 10 million assays.

[Slide.]

I would just like to acknowledge all these people. There are some people missing on here. John Finlayson, Ed

Tabor, Jay Epstein, Hira Nakhasi sort of cut through, made things very clear, made me see the wood for the trees.

Dr. Hsia did the work on the nanograms at cutoff and the viral load at cutoff. Guang Gao and Elliot Cowan helped me with the PowerPoint. Mike Busch, Megan Laycock, David Wright, and George Schreiber did those wonderful modeling studies, and George Nemo and Paul McCurdy were in on the overall planning at an early stage.

So, thank you very much.

DR. NELSON: Thank you, Dr. Biswas.

Any comments, questions? Yes.

DR. BOYLE: I just have a technical question. When you are using the multiple samples from the same donor, are they treated as independent samples when you are creating confidence intervals?

DR. BISWAS: They are treated separately, yes.

DR. BOYLE: But I mean basically, are you assuming independence when you are calculating the confidence interval?

DR. BISWAS: I would have to ask David Wright to answer that one.

DR. WRIGHT: David Wright from Westat.

The qualitative analysis that Robin was talking about, it is the 10 panels. We are looking at the time until they seroconvert, so the data analysis is only looking

at the 10 days and looking at them independently, so the sample size is very small, but we did find some interesting results.

DR. SMALLWOOD: Mr. David Wright is from Westat and he is a guest of the committee, so that questions from the committee may be directed to Mr. Wright.

DR. NELSON: Mary.

DR. CHAMBERLAND: Robin, did you want to comment - in the slide where you presented results looking at the NAT assay, comparing detection in the pre-ramp-up and the ramp-up phases, you made a comment that it was perhaps surprising that the plasma pools being much larger, one would think that they would not be as sensitive at picking up evidence of HBV viremia compared with whole blood, but, in fact, I don't want to say the opposite, but they don't appear to be that different.

Do you want to comment on why that might be?

DR. BISWAS: Well, when you do these NAT studies, I mean the sensitivity depends also on, you know, when you get these results, it depends, of course, on the dilution of the actual sample that you are getting, but it also depends on the amount of material that you are actually processing.

What I am saying is basically is that the plasma, in particular, that plasma assay, they seem to be processing large volumes of the sample compared to the whole blood

assay. I mean it is something that we are sort of counterintuitive at first, but it is due to the volume, the intrinsic sensitivity of the individual assays that are being used.

DR. CHAMBERLAND: So, just to make sure I get this, so, in the large plasma pool, you know, 500-plus, individual components in these pools, in point of fact there is more per-sample input than in the whole blood smaller pools.

DR. BISWAS: Yes, that is right.

DR. CHAMBERLAND: Less concentrated or whatever.

DR. BISWAS: Right. That is certainly one of them, yes, I agree, yes, that is correct.

DR. LINDEN: Based on historical experience with other new tests, is there any possibility of giving any sort of ballpark estimate of when these new unlicensed surface antigen assays might be able to be licensed?

DR. BISWAS: I am sorry, Jeanne, the answer is kind of no. I wish I could, but no, I don't know.

DR. ALTER: It seems to me in all my years of coming to this meeting, I have never seen such definitive data, and it is clear that the new surface antigen assays are better than the old, that the pooling is not a big advantage over the new assays, and that single donation will give you some advantage, single donation testing.

One question I have is whether these data can be analyzed now for anticore assay, and I hope that were we to use the more sensitive surface antigen tests and some NAT format, use those two in combination, could we drop anticore testing. One would have to look, not only at the seroconversion panels, but also chronic low-level carriers, but are those kind of things being done with the same panel?

DR. BISWAS: Well, you know, we have to keep things simple. I mean as it was, it is quite complex, it was a very complex study and we wondered whether we should include sort of the anticore angle, and we decided not because we thought it would just make things more complicated, but you are absolutely right, I think that the more sensitive assays, more sensitive HBsAg assays and pooled NAT and single unit NAT, certainly single unit NAT, how will that impact on HBsAg testing and anticore.

You know, that is certainly something that we all need to look into, yes.

DR. ALTER: It would be very easy to tack onto this study.

DR. BISWAS: Yes.

DR. ALTER: Jay says if the samples exist.

DR. BISWAS: Yes, those samples are getting smaller and smaller.

DR. NELSON: Thank you.

We are a little bit behind, but not too bad. Now is the open public hearing, and there are five people who have requested to speak.

The first is Dr. Mary Koontz from Abbott Labs.

DR. KLAMYRNSKI: I am sorry. This is Matt Klamyrnski from Abbott Labs. In the interest of time we are going to decline to present. Dr. Koontz's presentation complements both Dr. Stramer and FDA's presentation. You all have a copy of it. So, in the interest of time, we will decline. Thank you.

DR. NELSON: Thank you. The second is Dr. Bruce Phelps from Chiron. Is Bruce here?

DR. PHELPS: I am pleased to have this opportunity to address the committee on a topic of utmost concern and importance, the safety of the nation's blood supply.

My name is Bruce Phelps, Vice President of Research and Development for Blood Testing, Division of Chiron Corporation, a leading biotechnology company committed to maintaining blood safety throughout the U.S. and the world.

I would like to first direct my remarks to the data presented here this morning by Dr. Busch, Dr. Stramer, and Dr. Biswas, and to the impact these and other findings will have on immediate and future blood screening standards.

The data appear to indicate what we have

maintained for some time, that NAT pool testing is at least as effective at closing the infectious window as the most sensitive antibody or antigen tests. Without compelling evidence to the contrary, the committee may want to weigh other considerations that enter into the equation prior to rendering its decision.

Either way, Chiron is prepared and willing to undertake a course of action that is consistent with the committee recommendation on the current role of HBV NAT. As to the future of HBV nucleic acid testing, however, we believe that there are clear indications that a decrease in pool size, instrument upgrades, and improved technical execution among other advances will ultimately result in superior sensitivity for NAT versus surface antigen testing.

As the committee is well aware, the blood testing industry, FDA, and academia alike have always been defined by their commitment to elevate screening standards with new and improved technologies.

The committee will recall that U.S. FDA policy under Dr. Kessler directed manufacturer and encouraged blood establishments to implement leading edge technology, to decrease the window period during which a donor is infectious, but found non-reactive by currently licensed screening methods.

Prior to that directive, and since, we have

witnessed a steady technological progression including monoclonal antibody and antigen-based technologies that has significantly improved the safety of the nation's blood supply, and it is clear that NAT is the next technological innovation in the area of blood screening safety.

Numerous scientific studies have demonstrated that NAT reduces the window periods of detection in HIV and HCV, and the data presented today suggests that that remains true for HBV NAT, as well. In fact, recent investigations indicate that genomic NAT, when used on individual donor samples, may close the HBV window by 50 percent or approximately four weeks when compared to currently available tests.

Moreover, the National Heart, Lung, and Blood Institute of the NIH has contracted with our partner, Gen-Probe, to develop NAT testing assays and automation. Combined, these factors have led to the development of NAT as the new world standard in blood screening technology and offer the promise of providing Americans with a blood supply that is safer from risk of HIV, HCV, and HBV transmission.

Chiron is committed to leading the way to substantial improvement in blood screening. We are currently involved in the development of what we believe will be the gold standard in blood testing, a fully automated triplex assay that will allow single blood

donations to be screened for HIV, HCV, and HBV in one nucleic acid test.

Such a system will offer unprecedented levels of sensitivity while providing additional economy and utility to our customers and their beneficiaries, but this will take time.

Chiron is preparing to supply the country with HBV NAT testing and would seek to do so with an effective and calculated implementation plan. In the interim, however, we can confidently support the continued use of the most sensitive HBsAg assays until such time that minipool or individual donor NAT can be fully implemented.

When the safety of the nation's blood supply is at stake, we all carry a responsibility to provide not only the best product available, but also the best strategy for its introduction.

Chiron remains committed to the ideals of this committee and today publicly presents its offer of partnership and cooperation.

Thank you, Mr. Chairman, and members of the committee for your attention. At this time I would be happy to answer any questions.

DR. NELSON: Questions? Thank you.

The next speaker is Dr. Louis Katz from the American Association of Blood Banks.

DR. KATZ: Thank you, Mr. Chairman.

The AABB is the professional society for over 8,000 individuals involved in blood banking and transfusion medicine and represents roughly 2,000 institutional members including community and Red Cross blood collection centers, hospital-based blood banks, and transfusion services as they collect, process, distribute, and transfuse blood and components and hematopoietic stem cells.

Our members are responsible for virtually all of the blood collected and more than 80 percent of the blood transfused in this country. For over 50 years, the AABB's highest priority has been to maintain and enhance the safety and availability of the nation's blood supply.

AABB is happy to provide its perspective on the specific issue related to HBV transmission by blood products and the broader issue of test selection for the improvement of blood safety.

We have heard very well derived comparative data that should allow the committee rational consideration of the utility of NAT screening of whole blood donors for window period infection with HBV. AABB will cooperate eagerly and in a timely manner with the orderly implementation of these technologies when appropriate assays are available.

More generally, we support the application of

sensitivity standards across the various donor screening platforms being considered for implementation now and in the future.

Test selection should be based on equivalent or greater sensitivity, and not the specific technology being used. Assuming that an assay for HBsAg can be shown to provide equivalent detection of potentially infectious donors to a nucleic acid-based test, there is no a priori reason to mandate exclusive use of the latter. Of course, if greater sensitivity and specificity are demonstrated, these considerations should drive the decision.

Considerations of specificity, logistics, and resolution, among others, should drive the choices among equivalently sensitive assays. We believe that the FDA can play an important facilitating role in adoption of this philosophy in the international blood community.

With regards to the specific questions posed to the question, we support lowering the lower release standard, and have no position on the question regarding two sensitivity standards for different indications.

DR. NELSON: Thank you. Any questions?

The next speaker is Dr. Celso Bianco from America's Blood Centers.

DR. BIANCO: Thank you. ABC is an association of 75 not-for-profit, community-based blood centers that

collect nearly half of the U.S. blood supply from volunteer blood donors. We thank FDA CBER for the opportunity to make public comments before the Blood Product Advisory Committee.

We commend FDA, Dr. Busch, Sue Stramer, the assay kit manufacturers, and all the individuals that contributed to the data that is being presented here.

The comparative approach provides us with the means to assess each assay on its own merits in terms of reducing the windows of seroconversion for hepatitis B infection and the potential risk that donors in the infectious window represent for the safety of the blood supply.

The data also show the substantial improvement that new technologies bring to the donor screening process. ABC hopes that manufacturers and FDA will work together to assist collecting facilities in implementing blood donor screening for HBV DNA and for the newer technologies that were presented today. As this process evolves, ABC members request that CBER and the committee take into account some important issues.

The introduction of a new screening test is more complex than the measurement of benefits achieved by improved sensitivity. We respectfully request that CBER work closely with test manufacturers and scientists in the field to assess the impact of the introduction of HBV NAT on

sample pooling schemes, automation, software, and the availability of short-dated products like platelets.

We also request that these assessments include donor management and reentry algorithms for whole blood donations as opposed to source plasma in the sense that they recognize the importance of blood donors and the deleterious impact that unwarranted deferrals have on the volunteer donor base.

We also urge CBER to establish consistent sensitivity standards, and we see that this is happening, for HBsAg, HBV NAT, and other technologies. We believe that this approach is more rational than the one that is taken by some European organizations that recommended screening of plasma used for further manufacture by HBV NAT without a clear focus on assay sensitivity, pool sizes, or whole blood donations.

Some U.S. derivative manufacturers have initiated HBV NAT screening under similar research protocols. We believe that consistent sensitivity standards assure safety regardless of technology. We believe that the focus on whole blood donations and apheresis will guarantee assay configurations that ensure the availability of short dated products.

Rapidity and sensitivity are less critical for products based on source plasma because the starting

materials are stored frozen and the final products are virally inactivated.

We understand the difficulties associated with sensitivity standards because of the not infrequent dissociation between levels of HBsAg and HBV DNA, and the occurrence of internal deletion variants of HBV. However, we believe that these difficulties can be overcome and that these standards will guarantee the introduction of assays that really enhance the safety of the blood supply.

Regarding the questions to the committee, we have a revised comment that we passed to the committee because it just includes the answers the questions.

Should FDA change lot release specifications? Our members say yes. We see this as an effective way to improve the donor screening process as technology improves.

Should FDA set two separate standards, one for plasma for further manufacture and a different one for whole blood and components? We have a little bit of trouble with that. We suggest an answer no, because we believe the public will not accept less stringent criteria for plasma for further manufacture than for whole blood.

In closing, we want to emphasize the commitment of ABC member centers to the introduction of HBV screening by NAT in the future. Our recent experience with the introduction of NAT screening for HCV and HIV shows that

this can be done.

We are committed to blood safety, but we are also committed to the preservation of the supply of safe volunteer blood donors to all patients in need, because no blood we believe is a real risk, not a theoretical risk, and it threatens patient care.

Thank you.

DR. NELSON: Thank you. Any questions for Dr. Bianco?

The final speaker is Dr. Paul Holland from the Sacramento Blood Center.

DR. HOLLAND: I would like to present some data from Japan which are germane to this discussion. You have the one data slide which is shown there both in your hands and it is on the web.

[Slide.]

In essence, Japan, as you heard, began testing using NAT several years ago. On the bottom line, compared to the RPHA, which is their hemagglutination test, they perform the NAT after screening for this.

What you see is when they were using pools of 500 on the bottom line there, then, they were able to identify 5 NAT positive units. They subsequently switched to a 50-pool size and their sensitivity is 100 copies per mL, so with a 50-pool size, any sample would have to have at least 5,000

copies per mL.

Looking at a little more than half a million donations, what you see is they picked up 68 NAT positive units that were missed by their current licensed test.

I think what is important about this slide is that 67 of the 68 were picked up by a chemiluminescent assay, and sort of fitting with what was said earlier, some of these are window period donations, but some are low level viremic carriers. In fact, in their population, the majority were these.

So, the point of this slide is that the newer methodologies can pick up most of the NAT positives when you compare it to a pool of 50. So, I think this emphasizes with real world testing of hundreds of thousands of donations, that pooled NAT is approximately equivalent to some of the newer unlicensed technologies.

[Slide.]

These are the investigators in Japan or at least two of the three that provided these data.

[Slide.]

This is the machine, the Prism that they used to pick up those additional ones.

[Slide.]

This is Dr. Nuchprian from the Thai Red Cross.

[Slide.]

This is dated August of '96, and you see there they have the Prism in place there to pick up those HBsAg positives.

Thank you.

DR. NELSON: Thank you, Dr. Holland. Any questions or comments?

Presumably, the ones that were low level positive would currently be core antibody positive.

DR. HOLLAND: Yes. It is interesting, they actually use a core test there, but they use it on a titer level, so these escaped. They obviously didn't have high titer anticore because they escaped that test. They had low levels of anticore.

DR. STRAMER: I don't have a comment for Dr. Holland, but I think there was one more comment from the Red Cross that may have got missed in your list for the open public hearing.

DR. NELSON: You wanted to comment?

DR. STRAMER: I don't, but Dr. Rebecca Haley will.

DR. NELSON: I am sorry.

DR. HALEY: Mr. Chairman and members of the committee, I am pleased to be allowed to discuss the American Red Cross position regarding the comparative sensitivity of hepatitis B virus screening tests including tests for hepatitis B surface antigen and NAT and their

impact on the safety of the nation's blood supply.

I am Rebecca Haley and I am the Chief Medical Officer for the American Red Cross. The safety of the blood supply and the patients we serve is the number one priority of the Red Cross. Although transfusions in the United States are safer today than ever before, the Red Cross is committed to further improvements in donor screening through the use of ever more sensitive tests.

Currently, blood establishments in the United States screen for HBV by two methods. Hepatitis B surface antigen tests screen for HBV by identifying the presence of the HBV coat or antigen as the first detectable marker of HBV infection.

Additionally, blood establishments use the hepatitis B core antibody test to detect samples in the anti-HBC window period which is the time between the disappearance of the detectable hepatitis B surface antigen and the appearance of anti-HBs, the antibody that confers immunity.

HBV can cause inflammation of the liver, making some people acutely ill. Most individuals recover completely and test negative for HBsAg within four months, but a small percentage become chronic carriers.

Presently, tests licensed by the Food and Drug Administration to detect HBV in donors are generally not as

sensitive as those that are commercially available in Europe and in Japan, as Dr. Holland showed us.

The Red Cross has provided data to the FDA that demonstrates certain unlicensed tests for HBV screening are, in fact, more sensitive than the currently licensed tests. These include next generation HBsAg and NAT.

Red Cross data indicate that the next generation of HBsAg tests may be as sensitive as research-based pooled NAT tests, depending on the pool size and the sensitivity of the NAT method used. From a current good manufacturing perspective, the Red Cross believes that next generation HBsAg testing is the preferred method since pooled NAT, at present, is not available for use in the whole blood banking environment and the NAT processes introduced under IND lack essential process control features to ensure that errors are minimized.

Furthermore, NAT is presently labor intensive and lacks automation, resulting in the potential for human errors. The most important issue, however, is that pooled NAT will not identify the vast majority of HBsAg negative, HBV DNA-positive samples, most of which may have very low viral loads.

Until such time as there is an available NAT method with adequate sensitivity that will likely involve individual donation testing, the Red Cross is committed to

taking steps to improving blood donors for screening for HBV. Next generation HBsAg testing is such a step.

The Red Cross and the FDA data presented here today on the use of the next generation HBsAg represent an improvement that would increase detection and shorten the HBV window period. The American Red Cross calls upon the FDA to move expeditiously to license these more sensitive testing methods.

Furthermore, we urge manufacturers to conduct additional research and development on HBV NAT to automate this testing. These steps will further enhance the safety of the blood supply for the patients we serve.

Thank you for the opportunity to provide the views of the Red Cross on this important topic and I would be happy to answer any questions you may have.

DR. NELSON: Thank you, Dr. Haley.

Toby?

DR. SIMON: Dr. Haley, do you have a position from the Red Cross on the two questions to the committee?

DR. HALEY: No. The AABB covered that for us, and we certainly have contributed to the AABB statement.

DR. SIMON: No position, I believe.

DR. NELSON: Are there any other questions or comments?

Why don't we take a break. It is now 18 minutes

of 11:00. Why don't we take a break until 11:15 and then we will reconvene.

Open Committee Discussion and Recommendations

DR. NELSON: This session is for open committee discussion and to discuss specifically the data presented in relation to the questions asked of the committee by the FDA.

DR. NELSON: Dr. Biswas, can you ask us our questions?

DR. BISWAS: Question 1. As tests for HBsAg continue to increase in sensitivity, should FDA change the lot release specifications for licensed HBsAg tests in regard to lower limits of detection?

The second question. Inasmuch as products from pooled plasma undergo validated viral inactivation/removal steps during their manufacture, whereas whole blood and components are not subject to such steps, should FDA set two separate standards for the lower limits of detectability of HBV DNA in individual donations: one standard for plasma for further manufacture and a different standard for whole blood and components?

DR. NELSON: Are there comments by the committee or questions to Dr. Biswas about the questions? I think the questions are fairly clear. Yes.

DR. BOYLE: Could I just ask how Question No. 1 would work, or phrased differently, if the FDA changed the

lot release specifications for licensed tests, what would then happen, they would have to recertify themselves or--

DR. NELSON: Presumably, some or maybe many of the currently licensed tests would not meet the specifications.

DR. BOYLE: And they would then go off the market.

DR. NELSON: Presumably, unless--

DR. BISWAS: Those lots would not be released.

DR. NELSON: Unless we voted yes to the second question in which case they could be used for pooled plasma products. I think it is a good question in the sense that there may be other factors that determine whether or not the tests that meet the specifications and are used, are a pooled NAT assay, a single unit NAT assay, or a more sensitive surface antigen test, and I think that kind of makes sense to me to question the committee about the standard rather than the test because, as has been pointed out, there are other things and how quick you can get the results and the pooling and the performance, and maybe other things that relate to which specific test, by which specific blood collection facility is used.

So, that is the way I understand the question at the moment.

DR. KOERPER: What is the present lot specification for lower limit of detection, and are we being asked to set a new lower limit or just to say that we would

like the FDA to lower it? What is the present one?

DR. NELSON: We are not setting a unit today, but I think philosophically, saying as the tests show good performance, et cetera, that they should be.

DR. BISWAS: Yes, that is right, Dr. Nelson. The current sort of set limit is that they have to detect 1 nanogram per mL.

DR. NELSON: So, the limit from some of the data that was presented could be a log or approximately a log lower depending on what the performance was.

DR. BISWAS: Well, if one went to 0.1 nanogram, that could introduce a very difficult situation, of course. I mean what we are going to do, in fact, is pour over the data. I mean this was very much an interim analysis because we haven't used all the HBsAg tests, all the procedures that are available, and one would also have to take into account the impact that a lower limit would have.

DR. EPSTEIN: I just wanted to clarify why we are asking this question. What we are really saying is, is the committee sufficiently impressed by the apparent advancement in technology, such that it would warrant a new era where companies whose products could not pass a revised panel would have to reengineer their products or not sell them.

What you have seen is that with these limited numbers of samples tested and limited replicates, but a

series of data from different sources, that there are some assays in the pipeline that would appear to have 5-fold or 10-fold improvement in sensitivity.

So, we are asking is that enough to warrant changing the era of what FDA will accept.

DR. NELSON: All right. There was impressive data on improved sensitivity both by NAT and surface antigen.

DR. KOERPER: How does 1 nanogram per mL equate to viral particles per mL?

DR. BISWAS: I just don't have it at the top of my head, unfortunately.

DR. NELSON: The other issue, too, is that Dr. Busch showed us that during the ramp-up in seroconversion phase, there was a pretty parallel after the adjustment between the DNA and the surface antigen, but I think that may not be the case at different times in the natural history of the infection.

Obviously, with core being licensed that maybe it isn't as much an issue, but if later the consideration was to drop the core testing, then, there might be a reconsideration. We may have to see what would be appropriate at that stage, but that is not really the question right now with the current situation, it is just should we change the standard given the data presented.

DR. SCHMIDT: Could we translate this question

into sort of a summary of what we saw, how many cases of hepatitis prevented by going to the 0.5, for example?

DR. BISWAS: Well, what I had said in the last slide was that if one moved to more sensitive HBsAg tests, the yield would be 15 to 21 per 10,000 donations--10 million, I am sorry, 10 million, 15 to 21 if we went to the newer HBsAg tests, you know, the newer HBsAg tests being sort of in the ballpark of 0.2 to 0.1.

DR. NELSON: On the other hand, I still think the advantage is that it does provide a better margin of safety, and we have certainly had changes in the demographics of the population, such that we can't assure that the risks in the donor population 10 years from now will be the same as it is now, so if all is equal, a more sensitive and equally specific test I think would certainly be an advantage, at least that is the way I read it.

I think that acute hepatitis B infection from a blood transfusion, whereas, you know, it may sometimes be benign, it isn't always. In a hospital that I worked at 15 years ago, a laboratory worker acquired acute hepatitis B from a blood sample. She worked in the biochemistry department. She got acute hepatitis and died.

You know, this can happen, and I think it is a potentially serious and very preventable infection both with screening and with vaccine. I don't see a down side to

changing the licensure standard toward a more sensitive assay at this point since it is feasible.

DR. BOYLE: Just one observation I would like to make from the data, and that is, I think it was a very impressive presentation, I thought it was a good study that was presented, but when we are looking at differences between products where in one particular case there is a window period difference of 12 days, but it is not significant because of small sample size and variability, yet, you have got another one where the window period difference is two days and it is significant because of different levels of variability, then, I certainly hope we have big enough samples to be able to make determinations of real differences between products.

So, I am very glad we are not making the decision of what the level is, and I certainly hope that caution is exercised with changing those levels, but I think the data presented certainly indicates that we are moving in a different direction.

DR. NELSON: Presumably, in developing the standard since the FDA would have to look at the data, the feasibility, the products, et cetera, and the standard would be in nanograms for surface antigen and be in genome equivalence for a NAT assay, and that those two, if it is optional, one or the other, that they would be equivalent,

hopefully correct.

DR. SIMON: I, too, am impressed by the data, and I think that what I am understanding is from the comments that have been made from the FDA, and from the presenters, is that as we move along and some of these new assays become licensed, the FDA could then institute these new lot release specifications, and they are asking the committee then, when this occurs, and some of the older tests are not approved, is that acceptable, and I think most of us appear to be weighing in on the side of saying yes, that we do see this as a sea change or a generational change, or whatever terminology one wants to use, it would justify changing the lot release specification as new assays became licensed and available.

DR. NELSON: I guess the other point that should be made, too, is that although the numbers aren't large, if you compare the estimate of how many hepatitis B transmissions there are with how many HIV and hepatitis C, the numbers for B are larger even though the consequences may be different in the quality life years and all that kind of thing, nonetheless, the numbers are larger, and given the larger numbers, there can be a case like the one that I saw when I was in Chicago, that can have very adverse consequences.

Estimating what the outcome is with small numbers

is always a hazard, but this is a serious infection irrespective of--and it is worth preventing for sure.

DR. KOFF: I would love to see some more data that would support or possibly refute the notion that was raised I think earlier about what do we know about the infectivity of samples obtained in this very early phase.

I don't think we have a whole lot of information. We have some anecdotal information, I think mainly, but this is something that clearly could be studied with great difficulty, obviously, in chimpanzees because of the cost and limited availability, but we are calculating the number of infections averted assuming 100 percent infection rate, and that may be correct, but I am not sure that that really is the right number.

DR. SIMON: Could I just address this question to Dr. Koff, is that more germane to the issue of whether you add NAT rather than the sensitivity of the antigen test?

DR. KOFF: It may well be, I am not sure. In other words, if your antigen test sensitivity goes down dramatically, how many of those specimens, in fact, will be HBV DNA positive, and are they truly infectious? I don't think I know that information.

DR. NELSON: There are data both from REDDS and from the FACTS study, and so on, that transmission of hepatitis B from current surface antigen negative units.

Again, in both, that was a higher rate than hepatitis C or HIV using the current screening test.

That doesn't tell us about the pre-ramp-up phase, but I mean I think we have to assume given a unit of blood, now, given a product that has been through a plasma pooling or something like that, it may be different, but I would say given a unit of blood, I would suspect that any one in the pre-seroconversion or the ramp-up or pre-ramp-up, we would have to assume that there is a pretty good chance it's infectious. That would be my conclusion.

Do you agree, Mike?

DR. BUSCH: Yes, and it is complex and there is not a ton of data, but certainly there have been extensive, well, historical titration studies where either again front end sort of acute HBV viremic samples or chronic carrier samples have been titered out, and those titration serially tranfused into chimps, and those data support a relationship of about 10 genome equivalents per infectious unit.

Now, the numbers we are talking about are being expressed as genome equivalents per mL, and the question is whether, you know, the concentration is critical or the absolute number of viral particles that are transfused.

In talking to Fred Prince about this, his assessment is that it is the absolute number, that the liver is an incredible filter, it will concentrate the virus no

matter what volume it is diluted in, so in his assessment, as few as 10 genome equivalents in a transfusion is probably enough to transmit.

The typical unit of blood, you know, red cell or platelet component, will have 20 to 50 mL's of plasma, so probably there is infectivity even below the limit of NAT detection, and there is some suggestive data from one study from the Netherlands where they detected a HBV seroconverter, and they had samples back. They documented the transmission from a prior donation about a month or two earlier that was completely negative by HBV NAT assays.

Also, all the modeling that we are doing for yield in the individual donation phase that would be missed by minipool are only focused on the ramp-up component of that, so we haven't factored in what might be additional yield due to this smoldering viremia that will be intermittently detected stochastically by NAT.

On the front end, I think that those are the issues. In terms of anticore, there you often have either low levels or absent surface antigen, and you can have HBV DNA present in those samples. Some limited data again from Fred Prince in the chimps shows that those do not transmit. You have got so much complexed antibody that, in fact, the infectivity in that side of the HBV infection phase probably is much lower than reflected by the DNA copy.

DR. NELSON: I recall also that Jules Dienstag reported some years ago from hospital workers with needle sticks of surface antigen carriers. Now, this wasn't NAT, but some of the them were actually vaccinated. They got a surface antibody response, no core, no evidence of active infection. But I think that probably doesn't apply to the ramp-up stage where there is no neutralizing antibody and that kind of thing, so that in the various stages, the tests may behave differently.

Is the committee interested in voting on the first question or do you want to discuss it some more? Okay.

Do you want to read it again?

DR. BISWAS: As tests for HBsAg continue to increase in sensitivity, should FDA change the lot release specifications for licensed HBsAg tests in regard to lower limits of detection?

DR. NELSON: How many voting members would vote "yes" to that question?

[Show of hands.]

DR. NELSON: "No" votes?

[No response.]

DR. NELSON: Abstentions?

[No response.]

DR. SMALLWOOD: The results of voting for Question No. 1, there were 14 "yes" votes, there were no "no" votes,

not abstentions, and the voting strength of 14.

DR. NELSON: Also, the consumer and industry representatives?

MS. KNOWLES: Yes.

DR. SIMON: Yes.

DR. NELSON: Thank you.

Let's move to the second question. Do you want to read it?

DR. BISWAS: Inasmuch as products from pooled plasma undergo validated viral inactivation/removal steps during their manufacture, whereas whole blood and components are not subject to such steps, should FDA set two separate standards for the lower limits of detectability of HBV DNA in individual donations: one standard for plasma for further manufacture and a different standard for whole blood and components?

DR. NELSON: I think perhaps we need to discuss this question a little bit before we vote. It may be not as straightforward.

DR. SIMON: I have tried to get the thinking of industry in a position that I can state to the committee, and it is a little bit divided or inconclusive, but I think, on the whole, I would support the question and urge the committee to support the question.

I think there is enough scientific information and

practical clinical information about the infectivity of the two different types of treatment, that is, the whole blood and the components versus the fractionated derivatives, to indicate that it is justified to have two separate standards, and one does need to lower the limit of detectability of HBV DNA for plasma for further manufacture given the way that product is treated and the viral inactivation removal steps.

So, I think it is logical to have two separate standards in this case.

DR. NELSON: Marion.

DR. KOERPER: On the other hand, there have been many examples of slip-ups during the manufacturing process, and there have been transmissions of viruses that theoretically should have been destroyed by the heating, the solvent detergent, and the filtration.

So, I would argue that the recipients of these components deserve at least a safe a supply of blood as the recipients of whole blood and that we should set equivalent standards for both types of products.

DR. BOYLE: I would like to echo those comments. Two pieces of information. One thing we heard today was that the incidence, if I heard it correctly, of HBV in plasma donors was four times as common as in whole blood donors, which would lead us to worry somewhat about the

donors themselves, and the second thing that we usually discuss at these meetings is good manufacturing practices and failure of good manufacturing practices and why we cannot rely on the treatment alone to make it safe.

So, I would certainly be wary of establishing different standards for the two products.

DR. NELSON: Mark.

DR. MITCHELL: I believe that there should be two separate standards because, for example, I am very concerned about children with sickle cell that may receive four units of blood every month or every two months from the time they are babies through their adult life, and they are being exposed to a lot of whole blood, and the whole blood does not have the protections that the manufactured cells do, and I think that it is important that we try to equalize the protection of the blood and therefore, if we equalize the protection, it may call for increased protection on whole blood and products that do not have viral inactivation, so I think that we could very easily justify that.

DR. NELSON: So, you are arguing for there being two sets of standards?

DR. MITCHELL: That is correct.

DR. NELSON: Ed.

DR. TABOR: Not to detract from the importance of GMPs and our prior discussions, but I would just like to