true, the likelihood of a transcription error could occur, but then having a follow-up sample and a subsequent donation, the question of having an error on one donor two times in a row I think is incredibly remote.

DR. NELSON: Yes?

DR. CHAMBERLAND: Sue, what is your view or opinion about the interval of time that would be prudent to consider for follow-up testing, particularly for HIV? The FDA proposed algorithm states eight weeks, and then Mike Busch in his previous recommendation voiced a view for a more conservative six months. Just because we are going to be asked to look at that--

DR. STRAMER: I understand.

DR. CHAMBERLAND: --and I wanted to engage in a little bit of discussion on that.

DR. STRAMER: Fifty-six days would appear to be sufficient and very adequate for HIV. I mean, seroconversion occurs very, very quickly, and in fact in the Red Cross statements we will say 56 days for HIV is in fact what we support.

However, probably for simplicity, six months just makes the process consistent, that we do six months for HIV, we do six months for HCV, no

one has to do any thinking. I mean, that's what the standard algorithm is. It just represents consistency. But certainly biologically eight weeks is more than adequate. Exactly.

DR. CHAMBERLAND: I just wanted, I guess I wanted to make sure that I understood the data that had been presented correctly, and I hope I'm not misinterpreting anything that Mike presented, but at least what I thought I saw and understood, it would seem biologically that you could really go with an eight-week period.

DR. STRAMER: HIV seroconversion is completely reproducible.

DR. CHAMBERLAND: Right.

DR. STRAMER: I mean, through the 10 or 15 years that we've been looking at HIV seroconversion, it's been a reproducible event. I mean, the 2 out of 51 needle sticks are the only two exceptions.

DR. BUSCH: What I've tried to do is discriminate. If you're HIV RNA or antigen reactive and antibody negative, I also felt eight weeks was adequate time to seroconversion. That's a very conservative and adequate period.

What I tried to differentiate was, if

you're HIV antibody reactive and NAT negative, there I just--it's not so much that I think any of these people are infected. It's more a matter of letting that false seroreactivity dissipate, and that waiting six months--otherwise, if you test them too soon, you're going to be running the same reagents and you're going to get a double hit on two bleeds, and then they're permanently deferred or you have to start over.

DR. STRAMER: Although from studies that have been in the literature, p24 indeterminacy, for example, on Western Blot, will remain for years. So in many of these cases it doesn't matter if we wait 6 months or 10 years, people with persistent indeterminacy will remain quite EIA reactive.

DR. CHAMBERLAND: Right, and in fact the draft public or the draft CDC revised guidelines for HIV testing and counseling, not geared for donor testing, obviously, and do not include provisions as we have in blood donor testing for NAT testing, are going to recommend that if an individual tests EIA repeat reactive and Western Blot indeterminate, testing within four weeks, if it has not progressed, these people should be counseled that basically they are negative.

DR. STRAMER: That's right.

DR. CHAMBERLAND: But, again, I think that might on surface appear discrepant or confusing, but it's an entirely different setting without the benefit of NAT testing, which is what you say kind of mixes it up a bit.

DR. NELSON: Actually, I could see where if the reentry would require retesting a new donation, so that there would be two tests, you could accomplish both by retesting the blood at 56 days, thereby reassuring the donor but not actually taking another unit of blood to be retested for six months. Because I can see that when somebody was told that they may be HIV positive, come back in six months, that's kind of a pretty bad message. I mean, you know,they may have gone crazy in that time. The quicker we could reassure people, the better, but we could wait to reenter the donor, I would think.

Okay, any--oh, John?

DR. BOYLE: Just one last question. Since the purpose of this is to save the donor, not save the donation, is it possible to reenter the donor without reentering the blood?

DR. STRAMER: Well, that's what a follow-

up sample is supposed to establish.

DR. BOYLE: But I'm thinking about on a permanent basis.

DR. STRAMER: Well, if you're reentered as a donor and that donor is not going to say, "I'm coming in for my next blood donation. I mean, I saw an appeal on TV and I want to make my contribution."

DR. BOYLE: And you said it's a relatively small number, and they give their blood, and you don't use it.

DR. NELSON: And then the donor finds out that you threw away that blood that they took, and he's not very happy.

DR. EPSTEIN: The question whether to treat the units of those donors differently was the subject of an NIH consensus conference in 1985, and it was felt to be unethical. You know, given the fact that we don't have conclusive results about serologic findings, if we're going to discard units, we tell donors that they're deferred. Conversely, if we reenter donors, we mean they're safe and we accept their donations.

DR. HOLLINGER: Sue, I have a couple of questions. Back to the issue on the viral bands on

Western Blots, viral bands positive, GP 120, 160, etcetera. You mentioned that you thought that these were false positive, and I'm assuming that they probably are, but do we know for a fact that they're false positive?

You know, we assume that everybody with HIV remains infected and usually does not resolve their infection. Of course, if we make that assumption, then everything that we find like this becomes a false positive, when in reality it may not occur that way. Do you honestly believe these are truly false positive results, or--

DR. STRAMER: Yes, I honestly believe that, and you don't have to, whether I'm honest or dishonest. There are other data sets that have followed up these types of donors to demonstrate that these are false positives, as published by the REDS Group in JAMA. There is a larger Red Cross data set that demonstrates the same phenomenon.

And these donors, although I haven't had time yet, I will enter into a follow-up study to demonstrate that these are in fact false positives, especially those that were positive for Western Blot high level EIA, that were NAT negative even by PCR. I mean, we want to understand what's the

status of these donors, why do they test NAT positive but have blazing antibody responses.

DR. HOLLINGER: Okay. The other one has to do with, just for my own information, if you would, those two donors that did not seroconvert--

DR. STRAMER: Yes, the immunosilent HCVs, yes.

DR. HOLLINGER: Yes. I've got some questions about that. Maybe you don't know the answers because you haven't investigated enough yet.

But the first one was that, on the ones that did not seroconvert, were they tested with several different EIA assays? That's the first one.

DR. STRAMER: Yes. They were tested with both FDA-licensed HCV antibody assays.

DR. HOLLINGER: And they were negative for both, both of those?

DR. STRAMER: Correct. And negative by RIBA.

DR. HOLLINGER: Did you look for cryoglobulins in these individuals that might have--

DR. STRAMER: Yes, and we've looked for T

cell responses, as well, and these both have healthy, normal immune globulin responses, and actually T cell responses to other toxoids that have been looked at, but we haven't found a T cell response for HCV in these individuals, either.

DR. HOLLINGER: Okay, but not cryoglobulins? I'm really looking for specifically cryoglobulin.

DR. STRAMER: No.

DR. HOLLINGER: What about their ALT levels?

DR. STRAMER: ALT levels have been flat.

DR. HOLLINGER: They've been normal?

DR. STRAMER: Yes, like 14, 20. I mean, we have sampled ALT every time we get a follow-up. Other than NAT, by PCR and TMA, these donors would have no idea that they are HCV positive, and both have been repeat donors.

DR. HOLLINGER: And has the genomic map been looked at in either one of those, to see what material or what is really being detected, and what portion? Is this a nonstructural portion of the--

DR. STRAMER: No, we have not yet done that.

DR. HOLLINGER: So it has not been looked

at?

DR. STRAMER: No.

DR. HOLLINGER: Okay. Thank you.

DR. STRAMER: We have lots of samples, if you would like to collaborate with us.

DR. HOLLINGER: Thank you.

DR. NELSON: All right.

DR. KOFF: I wondered, again for general information, of 100 donors who are notified that they are HCV RNA positive by NAT testing, what proportion of them have not gone back to the Red Cross but in fact have sought medical advice? Do you have follow-up information on what happens?

DR. STRAMER: The only follow-up information that I can give you, and I would assume one analyte is no different than another analyte, is for p24 antigen, because we do have a very active follow-up program and we do reinstate for p24 antigen. And we know only about 30 percent of donors do actually go through the whole process, so again the yield, even if I show you absolute numbers that are low, they further diminish because of the small numbers that actually pursue this.

And of those, based on serological testing, that are biological false positives, the

vast majority still retain their biological false positivity. So even for the largest group of yield samples, productive donations that we will get from them will be few.

So even from the follow-up sample, if that tests reactive again for serology but not by NAT, what we will have to tell the donor is, "You have persistent false positivity. You haven't progressed to seroconversion. Your NAT remains negative. So you are otherwise healthy, but have some cross-reactivity to the test."

DR. KOFF: I was specifically more concerned about the hepatitis C story.

DR. STRAMER: I don't have specific data on how many actually pursue, you know, follow-up information. I mean, we would know that from the lookback information and the lookback endeavors that we have pursued, and we know the yield of those is incredibly small.

DR. FITZPATRICK: Sue, I wanted to follow up on Blaine's questions, on the case you're calling the--

DR. NELSON: Speak into the mike.

DR. FITZPATRICK: I'm sorry. On the case you're calling the abortive hepatitis C, there is a

single NAT positive sample and that's from the donation? Not to draw a red herring, but have you checked the donors that were collected at the same time, and can you be 100 percent sure it wasn't a bag or sample mix-up?

DR. STRAMER: What we did, not to go into--the husband of the donor called me and he was very anxious to have his wife cleared of her HCV infection, and he was so anxious that it made me suspicious. And all of the follow-up samples, because the tests were flat negative, my first guess was, we have two different individuals that we're testing here, and that's why we have a NAT positive followed by NAT negativity.

So we did--I have a plasma unit, so we did sensitive HLA, DNA tests from the follow-up samples, from two of the follow-up samples, and from the plasma. Within the confidence of the HLA tests we did, they typed to the same HLA types. So from the data we have, it looks like the follow-up samples and the first donation did come from the same individual. Because I said something's not right here.

DR. NELSON: I think that we're not going to get out of here much before midnight unless I

stop the discussion now, and I think I'd like to take a break now, before we have the next presentation. So let's try to be back at 11:15. That's a short break, maybe. Thanks.

[Recess.]

DR. NELSON: We have one more presentation before the open public hearing, and there are five people or groups of people who have asked to testify or give a talk at the public hearing, and then we have committee discussion on the proposed FDA reentry guidelines. And so I would ask, since we're--I want to give you a road map that we're actually probably an hour behind, so I'd ask the next speaker and those giving comments for the public hearing to be as concise as possible.

The next presentation, Susan Galel from Stanford University. Susan?

DR. GALEL: Thank you. Before I begin with the slides, I would just like to take a minute to address the question that seems to be recurring, as to why we want to reenter donors.

As a director of a blood center that does actively reenter donors, I would like to say that it is absolutely a donor retrieval issue, not just a donor counseling issue. When you consider that

we do seven infectious disease tests on every donation, and each test has changing performance over time, plus each manufacturer's test and each version of a test has a different donor population that it has false positive reactions with, you can see that your most dedicated donors over time are highly likely to have a false positive reaction on one or more of our tests, and we will lose our most dedicated donors if we keep permanently deferring them every time they have a false positive reaction. So I would like to make a plea for retaining the ability to reenter donors.

Now, in my other hat as a representative of the clinical trial, I will be reporting the experience of the 13 blood centers that have been performing the Roche AmpliScreen tests for HCV and HIV nucleic acid in pools of blood donors. This study is being performed at our blood center, Stanford University, plus 12 blood centers that are members of America's Blood Centers, and you can see that these centers are scattered throughout the United States.

In the Roche system, the original 24 samples are pooled through an intermediate plate into a master pool, and at the same time that the

pool is made by a Hamilton sample handler, the Hamilton also delivers an aliquot of each donor sample into an archive plate, and all resolution testing is performed from the archive plate, not from the original tube.

The master pool, the RNA is extracted from the master pool manually, and then is physically separated into two different tubes, and each tube is extracted for either--is amplified and detected for either HIV or HCV, using a fully automated amplification and detection system. So when we get a reaction in the Roche system, we know immediately whether it's an HIV or an HCV reaction because those detections are done separately, so there is no discriminatory NAT in the Roche system.

If the master pool is reactive, then we go back to the archive plate and we recreate new minipools of six members each, so we have four minipools of six members each, again do the manual sample RNA extraction and automated amplification and detection. In this case we only do the amplification and detection for the marker that was reactive on the master pool. And if a secondary pool is reactive, then we again go back to the archive plate, take samples from the individual

wells that were in that reactive pool, and extract, amplify and detect them individually, and identify the sample that was NAT reactive.

This is a data set from relatively early in the trial, at six months of experience. You can see that in this data set just under 2 percent of donations were included in a positive master pool, and just 1 in 1,000 donations were individual NAT reactive. And I should clarify that in this trial we are not permitted to treat seropositive samples different from seronegative samples, so they are mixed randomly in with, seropositives are mixed randomly in with all of our donor samples.

Looking at the donations that were individual NAT positive, meaning individual well from the archive plate, 90 percent of them were EIA reactive and 10 percent of them were EIA negative. Among the samples that were NAT positive, EIA negative, we had only 7 percent that appeared to be true positive, meaning that we were able to confirm NAT reactivity either on a specimen from the plasma of that unit, that is, the unit itself, or on follow-up samples. Fifty-seven percent of the samples appeared to be false positives, in that NAT performed on the plasma of the donation unit itself

or on follow-up or both tested negative for all HCV markers, and in this data set, about one-third of the samples we have no further information on.

Dr. Gary Tegmeier from the Blood Center of Greater Kansas City, which is one of our largest test sites, provided this detailed analysis of the false positive donors. This center has tested almost 1 million donations for HCV nucleic acid. They have identified eight donors which they believe are true positive, NAT reactive and EIA negative. By true positive, that means that we confirmed NAT reactivity on a second specimen from that donor, either from the--in seven cases it was confirmed on follow-up, and in one case the donor refused to enroll in follow-up, and the index donation was tested and it was NAT reactive. So this yield is about 1 in 123,000.

There were 48 samples that were NAT reactive, EIA negative, suspected to be due to contamination, in that NAT was negative on a second specimen, either the index donation itself or a follow-up, so that is a false positive rate or suspected false positive rate of about 1 in 20,000.

Now, looking at these suspected false positives, in 44 out of the 48 cases there was an

EIA positive, NAT positive, that is a true seroprevalent specimen somewhere else on the archive plate, and in half of those cases the true positive specimen was neighboring the false positive, that is, either next to or diagonally related to the false positive specimen.

Five samples appear to be contaminated when an archive plate was dropped. This was early in the trial, and the staff didn't realize the potential for splashing. The remainder of the suspected false positives occurred when there was a true positive, that is, an antibody positive, NAT positive, somewhere else on the archive plate.

In four cases there was no EIA positive, NAT positive specimen on the archive plate, and yet we have some other reason to think that this was a false positive reaction. In one case, further testing on tubes from the donors was all negative. In one case, tubes and the unit were tested and were negative. And in two cases, the tube, unit, and follow-up were all negative. So we don't know where that reactivity came from.

I would like to reiterate what Susan Stramer said about the potential for tubes being contaminated. Dr. Tegmeier evaluated the value of

going back to testing the original tube and trying to clear donor on the basis of that testing.

In 30 cases of the suspected false positive well on an archive--suspected contamination of the archive well, the tubes were negative, and in some of these cases the donors were tested by additional specimens and they are all negative. However, in 6 out of the 36 cases, the original tube was positive, suggesting that the contamination occurred not at the level of the archive plate but at the level of the tube. And in these cases, we still believe they are false positives because additional specimens from these donors were all negative.

And I would like to also reiterate what Susan said, that if you do supplemental NAT on these specimens they will be positive, so these are truly contaminated specimens, and doing supplemental NAT on a contaminated specimen should not be reason to defer the donor.

In 25 cases the units were available for testing from these suspected contaminated specimens, and they all tested negative. And nine of these donors for whom the units were available were enrolled in follow-up, and all of them were

negative consistently for all HCV markers on follow-up.

I would like to turn our attention to the donors that we think are true positives. We began to analyze this data after about 13 months into the trial, when we had screened about 5.5 million donations for hepatitis C nucleic acid. By that time we had accumulated 23 donors that we believed to be HCV NAT true positive, EIA negative, and the reason we thought they were true positive is that NAT reactivity was confirmed either on a follow-up specimen in the case of 19 donors, and in the case of four donors who refused to enroll in follow-up, the NAT reactivity was confirmed on the plasma of the index donation. So this overall yield is about 1 in 240,000, similar to what Sue Stramer reported.

However, when we segregated the yield data according to whether the laboratories had used the Abbott second generation antibody test as the screening test, versus using the Ortho third generation screening test as the antibody screen, we saw a dramatic and statistically significant difference in yield, a much higher yield for NAT testing, that is, NAT positive, apparent EIA negative, in laboratories that were using the

second generation Abbott EIA as the screening test of record.

We tried to get these index donations and retest these EIA 2.0 negative specimens using Ortho EIA 3.0, and 70 percent of them were reactive. That is, the PCR positive, EIA 2.0 negative, 70 percent of them were reactive by Ortho EIA 3.0, and therefore would not have been called PCR positive, EIA negative, had they been screened by a laboratory performing the Ortho EIA 3.0 assay.

From these 23 donors we had 19 that agreed to enroll in follow-up, and this slide shows you the progression of test positivity over time during follow-up. Among the donors enrolled in follow-up, eight were reactive for EIA 3.0, that is, they were EIA 2.0 negative but EIA 3.0 reactive on the index donation. One additional specimen was unavailable, the index donation was unavailable for EIA 3.0 testing, but a five-day follow-up was obtained and was reactive by EIA 3.0.

The remaining donors were nonreactive by both EIA 2.0 and EIA 3.0 on the index donation, but you can see they all became EIA 3.0 reactive promptly on follow-up. And I should point out that our follow-up was done at monthly intervals, so

these donations that were found to be EIA 3.0 reactive at 68 and 70 days could have converted earlier, but we only sampled the donors monthly. It might be more important to specify the date of the last negative test, and the last negative test that we have was obtained on day 39. So all I can say is, by day 70 all of our donors have become EIA 3.0 reactive.

However, the story is different when you look at EIA 2.0 reactivity. You can see that some donors have a very prolonged period in which they are EIA 3.0 reactive but EIA 2.0 negative, some more than six months.

In most cases the RIBA is also not positive for these donors. It is indeterminate, and consistently with a c33c band. In most cases, the RIBA changes from indeterminate to positive at about the same time that EIA 2.0 becomes reactive. In some cases, however, there is a difference, still a lag in time between EIA 2.0 reactivity and RIBA reactivity.

I cannot say for sure that all donors will eventually seroconvert to EIA 2.0. We do have some donors who are still EIA 2.0 negative after fairly significant periods of time.

The same data shown graphically makes it a little bit easier to see the patterns of seroconversion. Donors that are EIA 3.0 reactive on the index specimen but EIA 2.0 negative, many of them have a prolonged period before they become EIA 2.0 reactive, whereas among donors that are negative for all markers at the index donation, most of them seroconvert fairly promptly. And the laboratories that were using EIA 2.0 seem to be selectively enriching this donor population, that is, those who have the prolonged EIA 2.0 negative phase, although we can see one of those also among the samples that were negative for all markers at the index donation.

So, to summarize our observations of the follow-up study, about 30 percent of donors showed a significant time lapse of greater than 90 days between EIA 3.0 positivity compared to EIA 2.0 positivity, and during this EIA 3.0 positive/EIA 2.0 negative interval, almost all specimens are RIBA 3.0 indeterminate with a c33c pattern.

There is one case of a donor who was RIBA negative during this phase. The donor was EIA 3.0 positive, EIA 2.0 negative, RIBA negative, on two different specimens, days 17 and 54 of follow-up,

and became RIBA positive on day 115. So from this one sample it appears that EIA 3.0 is more sensitive than RIBA 3.0. And it is not clear from our follow-up whether all infected donors will ultimately become EIA 2.0 positive and RIBA positive.

Looking at the NAT reactivity among the follow-up specimens, again I want to report that all 19 donors became EIA 3.0 reactive by the second follow-up visit and by day 70. Five out of the 19, or about one-quarter of the donors, had one or more individual NAT negative samples during the follow-up period, but this is after they became EIA 3.0 reactive, so that every single follow-up sample was either EIA 3.0 reactive or NAT reactive.

Among the donors who had some negative NAT samples after they became EIA 3.0 reactive, three had a positive NAT on further testing, so that was an intermittent negative NAT that was reported by the other speakers. Two of the donors had two consecutive negative NAT samples after they became EIA 3.0 reactive, and they their follow-up was terminated because they had fully seroconverted, so we don't know if they have permanently cleared the virus or not.

Just to now update the data for our now two years of experience with HCV and one and a half years of experience with HIV, for HCV, we have screened 8.1 million donations for HCV nucleic acid. We have a total now of 32 cases which we believe are true NAT reactive, EIA negative, for an overall yield of 1 out of 253,000. Of these 32, we have 24 in follow-up, and in all cases every follow-up sample was either NAT positive or EIA 3.0 positive or both during the follow-up period.

In the trial we have about 300 suspected false positive reactions, for an overall rate of about 1 in 27,000, and we try to enroll these in follow-up. Among the donors in follow-up, we have 97 donors for whom we have obtained two or more follow-up samples with no evidence of infection, and 21 donors who had a negative unit that was tested and who were enrolled in follow-up with no evidence of infection.

And we believe that, therefore, if you have any one negative specimen, whether it be the original unit or a follow-up specimen that is negative by both EIA 3.0 and individual NAT, that that donor is uninfected. We have not yet had a person who tested completely negative on any

follow-up specimen, who later tested positive on a subsequent follow-up specimen. But I have to emphasize that that means we are talking about EIA 3.0. We certainly do have donors that are EIA 2.0 negative during follow-up, who are truly infected.

For HIV, we have screened approximately 5.4 million donations. We have one case that we believe is a true window case, that was reactive only for HIV NAT and negative for all other HIV markers. On the first follow-up specimen obtained 16 days after the index donation, the donor tested positive for everything: NAT, p24, and antibody and Western Blot. By day 24, the donor had become negative for p24 antigen but was still reactive for NAT and antibody.

Out of the 5.4 million donations, I have only been able to verify one suspected false positive donor. There may be more, but I'm having a little trouble getting that data. But at any rate, the prevalence of false positive reactions on the HIV NAT appears to be extremely low.

So just to apply this data to the questions that are being addressed to the committee, the first question: Is it useful to consider reentry for donors who had an individual

donation NAT positive reaction, anti-HCV EIA reactive, and RIBA 3.0 indeterminate or negative?

My answer, it's probably not, because in our experience donors who are NAT positive and RIBA indeterminate are most likely in the process of seroconverting. However, even donors who are NAT positive and RIBA negative may be seroconverting, and in our experience a false positive on both NAT and EIA is a rare event. However, it would be very, very easy to resolve these false positives by simply either testing the original unit or testing one follow-up specimen for both NAT and EIA 3.0. If the EIA 3.0 reactivity goes away, then that was a false positive EIA reaction.

Question 2: Should reentry be considered for donors who were NAT negative on pooled screening and serologically reactive with RIBA indeterminate results? And I would say probably not, unless you can--unless EIA reactivity goes away on an EIA 3.0 or more sensitive test. The concern is that these donors could be in the process of seroconverting. A negative result on pooled NAT is not necessarily comforting because pooled NAT is less sensitive than individual unit NAT, and we know from our data and the other two

speakers that some donors are intermittently NAT negative during seroconversion, and they may be RIBA indeterminate during seroconversion.

We do agree that individual NAT testing is useful for donor counseling for these donors, and if a second sample, a second pristine sample not subjected to the pooling process, is reactive for NAT, that that donor should be counseled as if they are positive. However, we disagree that a second NAT performed on the suspected contamination sample should be used for donor deferral or counseling.

And the question is whether some of these RIBA indeterminate donors may be uninfected, but it is true that probably the vast majority of RIBA indeterminate donors are uninfected, and I think it would be worth reconsidering when the next generation of screening tests is licensed, as long as the screening test is at least as sensitive as EIA 3.0. If the EIA reactivity goes away, then you don't have to worry about the indeterminate, the RIBA indeterminate reactivity, because it appears that EIA is actually more sensitive than RIBA.

Regarding the option of following up with an additional HCV NAT test at any time up to six months, we agree that testing of a second specimen

is extremely useful not just for donor counseling but for determining the true infectious status of the donor, and I believe that we and Sue Stramer would agree that the plasma from the index donation may be used for this purpose without need for bringing the donor in for follow-up, if the plasma is available and if the storage conditions were validated and approved by the manufacturer.

Additional testing of tubes from the original donation should not be used for decisions about donor deferral because they may be contaminated, and donors should not be deferred on the basis of a repeat or supplemental NAT on the original specimen because it was probably contaminated during the pooling process. We do agree that a NAT positive result on any second pristine specimen, whether it be the index donation itself or a follow-up specimen, should be cause for deferral.

Question 3: What should be the minimum time period for waiting for follow-up testing?

All of our window case donors for HCV were positive for either EIA 3.0 or individual NAT or both at every follow-up visit, so we would question whether any waiting period is required at all. All

of the donors were EIA 3.0 reactive by day 70. Most of them or eight of them were positive on the index specimen itself, and the remaining donors were positive on the first or second follow-up.

If you want to wait for the EIA to be reactive, eight weeks should be--I'm sorry--eight weeks should be sufficient for follow-up if you are using both individual NAT and EIA, and EIA 3.0 must be used for reentry purposes. If you want to allow enough time for EIA 3.0 to become positive, then six months should be more than sufficient, since all of our donors were reactive by day 70. We agree that RIBA should not be required for reentry so long as EIA 3.0 is negative, because RIBA 3.0 appears to be less sensitive than EIA 3.0.

The last HCV question: Should the blood establishment have the option of continuing to follow up a donor with individual sample NAT negative but persistent EIA reactivity? And the answer is, absolutely. Each manufacturer has a different donor population that it has false positive results on, and these donors may become nonreactive on the next generation screening test or on another manufacturer's licensed screen. So as long as the follow-up test has, follow-up EIA

has sensitivity at least equivalent to the original reacting test, then the donor should be reenterable.

And one request from members of our clinical trial group, since we are anticipating licensure of another technology which will not be called enzyme immunoassay, we would like for the reentry algorithm to use terminology that doesn't refer to EIA but rather to something like a licensed serologic screening assay, so that it will be applicable to the PRISM assay.

We have very little data on HIV because, as I showed you, we had only one true positive and one or very few false positives. But just looking at the antibody screen, this is data from just over 1 million donations from three of our trial sites, you can see that the vast majority of EIA, HIV EIA reactive specimens are negative by NAT and Western Blot negative or indeterminate.

Questions for HIV. Question 1: Is it useful to consider reentry for donors who are NAT positive, EIA reactive, and Western Blot indeterminate or negative?

The answer from our system is probably not, because in the Roche system false positive NAT

seems to be an extremely rare event, and the probability of false positive results on both EIA and NAT is extremely unlikely. However, again, it should be very easy to determine the infectious status of that donor from one follow-up visit.

Question 2: Should reentry be attempted for a donor who is pooled NAT negative, antibody reactive, and Western Blot indeterminate?

The answer is yes, not on the basis of data that I have presented today, but it is clear from the literature and data that were presented previously to this committee that most Western Blot indeterminate donors are uninfected.

Question 3: Follow-up testing prior to--sorry--What should the minimum time period be for waiting prior to follow-up testing?

We believe that follow-up testing prior to eight weeks or testing of the second specimen from the time of donation, something that was not exposed to the pooling process, may be very useful for donor counseling. For reentry, eight weeks should be sufficient based on the time period of EIA conversion after NAT reactivity appears, from published literature.

For Group 3 donors, that is, those who are

reactive only on an EIA and not on NAT, we would suggest that the donor could be reentered if the EIA reactivity disappears, that is, if you switch to another manufacturer's assay and the EIA reactivity disappears, that you may even be able to consider reentering the donor without doing an individual NAT, although it's certainly easy to do an individual NAT.

We agree that Western Blot should not be required if the repeat EIA is nonreactive, that the EIA alone should be sufficient for reentering the donor. And we agree that a positive individual NAT on a pristine specimen, but not a repeat NAT on the original contaminated specimen, should be cause for permanent deferral.

Last question: Should the blood establishment have the option of continuing to follow up a donor with NAT negative persistent EIA reactivity for potential reentry?

And the answer is, absolutely. The argument is same as for HCV, that this donor may be nonreactive on another licensed serologic screening assay, and so we should be able to reenter those donors if they are nonreactive by a screening assay of sensitivity at least equivalent to the reaction-

-to the test that they reacted on originally.

And one final comment, a request from some of the centers in our trial. We would like to make sure that IFA negative donors are included in the reentry strategy for HIV, since many centers use IFA instead of Western Blot as their HIV supplemental testing. I personally don't have data on IFA indeterminates, and I'm not aware of the data that would support or refute treating the indeterminates, IFA indeterminates, similar to blot indeterminates, but I understand that IFA indeterminates are a relatively rare event. And I think that's the last slide.

DR. NELSON: Thank you very much.

Are there questions?

My understanding is that the FDA proposed guidelines just say a multi-antigen test, not EIA 3.0. Is that correct, Paul?

DR. MIED: For HCV, yes, that's correct.

DR. NELSON: Right, so in view of these data, I think we may want to consider modifying the criteria. I think that was one of the most impressive and interesting new data that you presented.

Okay. I think if there are no questions,

and thank you very much, there are five people that wanted to make a presentation, and I would urge these speakers to be as brief as possible, particularly if their comments have already been covered or discussed by previous speakers.

OPEN PUBLIC DISCUSSION

The first, Dr. Chyang Fang from GenProbe/Chiron.

DR. CHYANG FANG: Thank you, Mr. Chairman. May I have my slides?

DR. NELSON: Are there problems? The machine took a break?

DR. CHYANG FANG: Thank you. Today we will present our pivotal clinical study data as it relates to the proposed donor reentry algorithm.

Background: In the study, a total of 191,648 donor samples were tested in 11,978 pools of 16. In pool testing, 175 or 1.46 percent of pools were reactive. All samples composing these reactive pools were tested individually. One hundred and forty-two pools contained at least one NAT reactive sample, and 33 pools contained no NAT reactive sample.

A total of 156 NAT reactive samples were identified in the study. All samples composing

negative pools, and negative samples from reactive pools, were considered negative. These units were released if also seronegative. This accounted for 99.91 percent of donations in the study.

Units associated with the 166 individually reactive samples were discarded. These donors were temporarily deferred, samples were further tested with the HIV-1 and HCV discriminatory NATs. Of these, 13 were positive only for HIV-1, and all 13 were also Western Blot positive. One hundred thirty-eight were positive only for HCV, which included 129 RIBA positive, 2 RIBA indeterminate, and 7 HCV EIA negative samples.

The remaining 15, or 0.008 percent of the total sample tested, were negative in both discriminatory assays. All 15 samples were retested in the HIV-1, HCV multiplex NAT and were negative. Based on the non-discriminate and repeat negative NAT results, the donor deferral on these 15 donors were reversed. This reversal of donor deferral differs from the FDA-proposed reentry algorithm. I'll present data later to support the fact that this non-discriminate NAT reactivity were false positives.

For the next two slides, I will show how

our clinical study data, including both samples tested first in pools and 640 samples tested individually, correlate to the proposed donor reentry algorithm, first for HIV and then for HCV.

For HIV there was one sample in Group 1. This sample was HIV EIA reactive, Western Blot indeterminate, but HIV-1 discriminate, NAT negative. It was HCV discriminate, NAT and RIBA positive. Therefore, the NAT reactivity was due to HCV, not HIV-1.

There were 156 HIV EIA negative samples in Group 2. Of these, 139 were positive only in the HCV discriminate NAT. The remaining 1 samples were those negative in both discriminatory assays. All were retested multiplex NAT negative.

There were 146 NAT negative, HIV EIA reactive samples in Group 3. Of these, 94 were Western Blot negative and 52 were Western Blot indeterminate. According to the study protocol, 48 available Western Blot indeterminate samples were tested with the supplemental NAT, and all were negative.

For HCV, two samples were in Group 1. Both samples were HCV discriminate, NAT positive, and RIBA indeterminate. According to the study

protocol, these two samples were considered true positive.

Thirty-seven samples were qualified for Group 2. Of these, 13 were HIV-1 discriminate, NAT positive only, and all 13 were also Western Blot positive. Seven were HCV discriminate, NAT positive only. These were potential yield cases, and donors were entered into the follow-up study which will be shown in the next slide. The remaining 17 were those samples that tested NAT negative in both HIV-1 and HCV discriminatory assays.

For Group 3, 136 samples were NAT negative and HCV EIA reactive. Of these, 92 were RIBA negative and 44 were RIBA indeterminate. Forty of these RIBA indeterminate samples were available for the supplemental NAT, and all were negative.

In this study there were 7 HCV NAT positive, EIA negative samples. Six of the seven were from two pools which each contained at least one HCV NAT positive, seropositive sample. Five of these donors returned once, 14 to 46 days after the index donation. for follow-up testing, and all were NAT negative and seronegative.

The bag plasma, if available, was used for

repeat NAT and/or supplemental NAT. The results show that at least some of these NAT false positive results were due to contamination of the original NAT tubes. Bag plasma for sample number six was also NAT positive. The serum sample of this donation was retested and found to be EIA reactive but negative in RIBA. Unfortunately, this donor declined follow-up.

In summary, the Chiron Procleix HIV-1/HCV assay demonstrated high specificity in the pivotal clinical study. Ninety-nine point nine one percent of donor samples tested negative. Zero point zero eight percent were NAT positive and seropositive. Based on the proposed algorithm, only 0.01 percent will be deferred based solely on NAT reactivity, and will be eligible for donor reentry.

Second, non-discriminate NAT reactivity were likely due to reaction tube contamination or technical errors, since these samples retested as NAT negative. According to the clinical study protocol, donations with these results were discarded but donors were not deferred.

In the military NAT blood screening program on individual samples from April to December of last year, there were 21 cases where a

donor with reactive, non-discriminate NAT results returned for follow-up testing or subsequent donation. Most of these visits took place between 50 to 100 days after the index donation.

Of these donors, three returned twice and two returned three times. The intervals between subsequent repeat visits ranged from nine days as for Case No. 17 to more than six months as for Case No. 21. All follow-up test results were NAT negative and seronegative, indicating that none of these donors were infected with either HIV-1 or HCV, and therefore the initial NAT reactivity was confirmed as false by test results on follow-up bleeds.

Finally, our clinical data results suggest that a qualified alternate sample of the index donation, such as plasma from the bag, may be useful for determining false positivity at index by repeat NAT and/or supplemental NAT, since most of the NAT false positive results were caused by sample-to-sample cross-contamination due to the pooling and/or the testing processes.

Thank you.

DR. NELSON: Thank you.

Comments? Questions? Okay. Thanks very

much.

The next person that has asked to speak, Dr. Celso Bianco for America's Blood Centers.

DR. BIANCO: Well, thank you for the opportunity to speak. America's Blood Centers is an association of 75 not-for-profit, community-based blood centers that collect nearly half of the U.S. blood supply from volunteer donors.

I would like, before I get into the real statement, to make a couple of additions. One, about the value of the reentry that has been discussed here, there is one side that is obviously the donor, and that is the most important side. There is also a side of the recipient that we have not talked about.

Essentially, all those that are identified as positive according to the criteria will lead to a lookback and notification of recipients and a request that those recipients be tested. Not infrequently, those recipients are tested, and even if they get test results, there remains that doubt that they could have received an infected unit, or even in legal cases. So in those cases also, having had negative data in the follow-up from these false positives, we have useful things.

The second thing is that the donors I think in recent years feel that they are being treated as raw materials, and I want to remind all of us that they are human beings and they think, they feel, and they cry.

And finally I want to thank particularly Dr. Paul Mied for having addressed many of the issues that I am going to raise here during his presentations.

I am not going to address the algorithm. I think several people did. But we are very concerned, ABC members, about the increasing complexity of the proposed algorithms for resolution of initial screening test results. Complexity discourages reentry and offers opportunity for error.

The victims of such complexity are the volunteer donors, who often are told that their results have no clinical significance, they are deferred for life to protect the health of the recipients. Most sophisticated donors have told us personally that this message is schizophrenic. Why can't they donate if they are not infected, if we are confident that they are not infected?

The requirement for additional samples

obtained outside the donation process for performance of reentry protocols also increases complexity without obvious benefits. There may be an impression that these samples--that the unit inside the system would represent some risk, but actually centers frequently have access to backup specimens and plasma units for performance of additional screening. Testing of those specimens should be allowed.

Specimens collected at a subsequent date require that the donor return exclusively for the purpose of being retested. Many donors are so frustrated at being deferred that they refuse to return. Moreover, when those samples are collected successfully, they must be processed separately, outside the well controlled environment of collections, manufacture, and distribution, computer controls, bar codes, and all that. It's a separate system.

It's our belief that they are subject to greater error than specimens that undergo routine screening. Furthermore, routine specimens obtained in the course of a blood donation are subjected to the entire battery of screening assays, providing a better picture of the infectious disease status of

the individual. So we would like to see the individuals coming back to donate, not just to give a sample.

Additional, more specific supplemental tests were very useful in the early days of HIV and HCV testing because of the low specificity of the available screening assays. Today, however, the licensed supplemental tests for HIV and for HCV are actually less sensitive and less specific than the initial screening tests. These supplemental assays also generate a percentage, a high percentage of the dreaded indeterminate test results. Donors with indeterminate test results are in eternal limbo.

There are better approaches for the resolution of repeatedly reactive screening tests. The most important one is being considered today as part of the algorithms that were discussed. It is time to seroconversion. Time is better than any confirmatory test that we have available in the market today.

Essentially, 100 percent of the HIV infected individuals become, after a short period of time, repeatedly reactive on currently licensed antibody screening tests. FDA recognized this fact

when it licensed the screening assay for HIV-1 p24 antigen, because donors who are negative on the antibody test are eligible to donate again after eight weeks for reentry.

The introduction of NAT for HIV made those algorithms redundant. A donor who is positive on NAT for HIV, and negative for HIV, should simply be allowed to donate after eight weeks. Neither the HIV-1 p24 antigen screening, the Western Blot, or the IFA contribute to the resolution of the initial result. Time and test repeat resolve the issue.

The same is true for HCV. The supplemental RIBA test does not contribute to the resolution of the initial screening test result. RIBA only complicates matters by generating indeterminate test results, such as those associated with NS-5, that have no significance.

An individual that is positive on NAT for HCV and positive on a third generation antibody assay for HCV, is positive, period, even if there are some aberrations. But in the absolute majority of the cases, these individuals should be deferred, lookback should be performed as soon as possible. There is no reason to wait for weeks for a RIBA test result.

Individuals who are positive on antibodies to HCV and negative on NAT should be eligible for reentry when NAT and new technologies become available. Individuals who are positive on NAT and negative for antibodies to HCV, to third generation, they should be allowed again in the future. Both groups will be screened again, using procedures that are more sensitive and more specific. In these cases, the requirement for a six-month interval between the reactive donation and the reentry donation would be sufficient to allow time for seroconversion.

In the case of screening tests for which there is no licensed supplemental test, donors should be automatically eligible to donate upon licensure of new or more sensitive and more specific technologies, because they will be rescreened with newer, more sensitive and more specific assays. The introduction of new technologies is a major opportunity to reenter donors, because the sources of false positive results are different from the old technology.

Thus, reentry algorithms should take this into account. The rule that is part of many of the FDA guidances, that an individual that had reactive

results on two separate occasions must be permanently deferred, should be eliminated because it does not contribute to recipient safety, particularly when the rule is applied to multiple tests performed on the same specimen. It only perpetuates errors.

Upon licensure of newer screening technologies such as NAT or chemiluminescence, that is, the PRISM, donors who were reactive on EIA and had negative supplemental tests should be eligible for reentry. This should also be true in the case of donors who were reactive on antibodies to HCV-2. They should be eligible to donate again, except for those with a positive NAT or RIBA results. This does not mean that their donations will be automatically accepted. They will always be subjected to the complete battery of screening assays. If negative in all assays, including the licensed NAT, their donations are suitable for transfusion.

NAT for HIV has totally obviated the already small value of HIV-1 p24 antigen tests. The amount of data documenting this fact is overwhelming. ABC members respectfully request that FDA eliminate the requirement for HIV p24

tests upon implementation of a licensed NAT test for HIV. In addition, ABC members request that individuals with more than one unconfirmed HIV-1 p24 antigen test result, because those were samples that were taken in the course of follow-up, also be allowed to donate again.

ABC member are looking forward to simpler, more rational confirmatory algorithms. We believe that simplicity reduces opportunity for errors, leads to more effective compliance, and consequently increases the safety of the blood supply.

Thank you for the opportunity to comment.

DR. NELSON: Thanks, Celso.

DR. BIANCO: If there are any questions, I will be glad to answer them.

DR. NELSON: Questions or comments for Celso?

Next on the list is, and I haven't seen him, Dr. Lou Katz representing American Association of Blood Banks. Lou looks different today.

[Laughter.]

Kay Gregory will be--

MS. GREGORY: Yes. Obviously I am not Dr. Lou Katz, but unfortunately at the last minute he

was unable to make the meeting, and since I am his right-hand person for our TTD Committee, you can guess who he called and said, "Guess what you get to do?"

The American Association of Blood Banks is the professional society for over 8,000 individuals involved in blood banking and transfusion medicine, and represents 2,000 institutional members, including community blood collection centers, hospital based blood banks, and transfusion services, as they collect, process, distribute, and transfuse blood and blood components and hematopoietic stem cells. Our members are responsible for virtually all of the blood collected in this country, and more than 80 percent of the blood transfused. 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.

I would like to thank the agency and the committee for this opportunity to address them.

The greatest value of HIV and HCV reentry has always been the sense of closure or certainty they provide the donor to whom the difficult message of false positive test results has been

given. Nevertheless, it is apparent from a survey of the major blood collection organizations conducted in preparation for this meeting, that reentry of donors with false reactivity for these two agents, while permitted by the FDA, is not universally embraced.

As you have already heard, the American Red Cross does not engage in donor reentry, and in a survey of members of America's Blood Centers that had a 57 percent response rate, 63 percent of the centers reenter for HIV and 63 percent for HCV, representing 63 percent and 80 of the donations to responding centers, respectively. These two organizations, the Red Cross and the ABC members, reflect over 95 percent of the volunteer donor blood collected and distributed in the United States.

The reasons that reentry is not universal are fairly straightforward. The regulatory implications of a mistake are substantial, and most of the activity, as already noted, is performed manually; that is, there are no computer controls. The algorithms, both available and proposed, are cumbersome and expensive relative to the number of donors salvaged. In particular, access to some of

the assays required for reentry is perceived as limited by some centers.

Persistent false serological reactivity makes the yield of salvaged donors low. Our ability to counsel donors effectively and allay the fear provided by false positive tests has improved greatly over long years of extensive experience. We have now added NAT in minipools to our arsenal of tests, allowing further refinement of the messages that we provide to donors.

As you have heard at this and prior meetings, the specificity of the systems in use in the U.S. is admirable. At Dr. Katz's center, which draws about 60,000 donations annually, they have had a single false positive HCV PCR in over two years of screening, and no false HIVs.

The draft algorithms provided by the FDA continue the tradition of complicated approaches to reentry of donors with clinically irrelevant test reactivity. The requirement for an interim visit for repeat testing is an example. We would prefer that use of an independent aliquot, including residual plasma appropriately stored from the index donation, be explored as an acceptable sample.

This would allow required testing and more

rapid resolution of false NAT reactivity without a second visit by the donor, and can open the door to a testing algorithm similar to those in use for anti-core and anti-HTLV 1/2, wherein the donor is not notified of clinically irrelevant results until they arise a second time. The medical director of the collection facility could make a medical determination of the need for further immediate diagnostic testing on a case-by-case basis.

With regard to the specific questions posed to the committee, in Question 1 we are asked about an event that must be incredibly rare, if it has yet been observed. It posits the existence of a population of donations that are simultaneously HIV or HCV false positive in both the screening antibody assay and NAT. While we will be happy to have the flexibility to reevaluate such donors, it's not a priority compared to other issues.

Question 2 relates to NAT negative donations with unconfirmed indeterminate repeat reactive serology. With regard to HIV, there is a large body of historical data and experience that tells us these donors are uninfected, using appropriate criteria on immunoblotting and IFA. They must certainly be given an opportunity for a

simple reentry.

Where HCV is concerned, a small proportion of donors with isolated c33c may be infected, and here there is a need to use single donor NAT to exclude real infection. Under any circumstance, if resolution testing on the index donation is inconsistent with infection, we would ask the committee to consider if follow-up testing at the specified interval is allowable on a donation, rather than requiring an independent visit just for a sample.

Question 3 addresses the minimum time period prior to reentry. This may be different, depending on the screening assay used to identify the donor. It is apparent that for HIV screening serologies in use currently, the standard eight-week interdonation interval for whole blood would work.

Where HCV is concerned, and the Abbott HCV 2.0 EIA is still widely used, there appear to be some individuals with delayed seroconversion and intermittent low-level viremia on NAT assays. The data on these donors will need careful scrutiny to select a minimum interval. This may not be an issue with EIA 3.0, nor with the PRISM

chemiluminescence assay, and the six months proposed in the draft algorithms would appear to be more than adequate.

Question No. 4 is fundamental to the relationship of collection facilities and donors. The answer is yes, this option must be available. With current and future testing algorithms as sensitive and specific as they are and will be, we need to be allowed, without complication, to take advantage of current licensed technology to provide closure to donors with aberrant test results. The ultimate closure is allowing the donor to return to the volunteer donor base.

Although not addressed in the algorithms proposed, we would like to see reentry of the substantial number of donors with repeatedly false positive and indeterminate HIV-1 p24 antigen reactivity, presuming the antigen test will no longer be required after licensure of NAT assays. We propose that donors historically deferred for repeatedly false reactivity with this marker be permitted to return for a donation, and reentry be allowed on the current test results, irrespective of the historical deferral.

A couple of smaller points we would

reiterate that have already been made. That is, you need to look carefully at the terminology that you are using, now that EIA and blot technologies are not the only mechanisms available for testing.

We appreciate the flexibility of the agency in providing an endangered species, the volunteer blood donors, simple reentry algorithms.

DR. NELSON: Any comments or questions from the committee?

Thank you.

The next person that has asked to speak, David Cavanaugh from The Committee of Ten Thousand.

MR. CAVANAUGH: Thank you, Dr. Nelson. I am Dave Cavanaugh, the government relations person for The Committee of Ten Thousand, and I am pleased to be able to be here. The Committee of Ten Thousand got its name from the fact that there were 20,000 people with hemophilia in 1980, and approximately half of them--sorry, is that signal better?

The Committee of Ten Thousand, the name is from the fact that there were approximately 20,000 people with hemophilia in 1980, and approximately 50 percent of them contracted HIV from the antihemophilic factor, their medicine, basically.

We are not ones to use acronyms and present slides with data ranges, but we saw a few things already this morning we were a little concerned about, and I have about a total of five points to make.

The concern arises from hearing, as consumers of, recipients of potentially contaminated blood, terms like "bang for the buck," terms like "probably not." I think there was-- we're very glad that NAT exists. It has obviously raised the bar quite a lot, and we appreciate that, and we know that in the work of the research field, the product is a sound professional research paper. However, even then we cannot say that we're overjoyed to hear that the main job is to tell donors they're healthy.

We are a little concerned that there was a lot of discussion of NAT pools, matrix pools, but not an acknowledgement of the blood products side of things. Blood products are manufactured in pools ranging from 50,000 units to 250,000 units, and a contaminated unit contaminates the pool, unlike in the NAT testing where they are all nice and discrete. And so we are very chary about the manufacturing process.

When we hear about collection centers or

see a collection center, we know that sometimes you'll see pictures of grateful donors in hospital beds receiving a good unit, and that's important. That's a motivator. But they don't show a person infusing hemophilic factor at home. You know, all of the consumers of blood products are very frequent consumers. They are not getting one transfusion after one car accident, ever. And again, as you know, that is what has made us very much at risk.

So that is what I would like to say. Thank you.

DR. NELSON: The next person is Bob Marks from the Hemophilia Federation of America.

MR. MARKS: Good morning. I'm here speaking on behalf of the Hemophilia Federation of America, and also as a consumer of the blood products that you're speaking of at this point in time.

While I understand the concern over an individual who has been tested false positive being reassured that their test results come back negative, and then being informed of that information, I'd like to bring three points that I believe are very important, at least for myself and

my community, the first being a question:

Did the number of units to be returned to the blood pool from the country warrant the amount of risk of one contaminated unit?

The second question I have: Does the assurance of those tests with the false positives and informed to be negative, outweigh that risk of just that one unit?

And lastly, I think one of the things that everybody up here should be considering when they make their decisions in this area is, if just that one unit of blood comes through, we're talking about your mother, your father, your wife, your husband, your son, your daughter. And to sit there and to think, "It can't happen to me, it won't happen to me," I assure that my mother and father never thought that it would happen to them, and I assure you I never thought that it would happen to me.

So to talk in terms of probably, maybe, we think so, one unit of blood is all it takes, and I think that needs to be the overriding consideration here, that we're talking about human lives, and dollar signs don't come into this.

Thank you.

DR. NELSON: Thank you very much.

Dr. Sue Stramer wanted to also present a statement from the American Red Cross.

DR. STRAMER: Thank you. Mr. Chairman and members of the committee, the American Red Cross would like to thank the FDA for the opportunity to address the issue of the reentry of donors deferred because of HIV or HCV NAT or serological test results.

At the March meeting of the BPAC this year, I presented data on the types, frequencies, and causes of NAT false positive test results, and how the false positive results relate to donor and product management. Earlier today I presented data on the number of donors who test false positive for either HIV or HCV within the three FDA categories. Data were also presented supporting reentry of those donors that test seronegative but NAT falsely reactive, that is, Group 2, and those donors who are NAT negative but test falsely reactive in screening tests for HIV or HCV, that is, Group 3.

The Red Cross has submitted to FDA a NAT donor reentry algorithm and supporting data through our Investigational New Drug amendments submitted in January 2000 and in February 2001. We have not

yet initiated donor reentry for donors testing falsely reactive on NAT, pending a written response from FDA as requested in our IND amendments, or pending formal FDA guidance.

We believe donor reentry algorithms, whether for NAT false positive donors or serology false positive donors, should be simple so that maximum yield is achieved, while at the same time ensuring maximum safety to the blood supply. They should require a single follow-up sample from the donor to ensure that they are in fact test negative prior to the collection of a subsequent unit.

They should include an interval between the reactive index donation and the subsequent donation, including the test negative follow-up sample, of six months for HCV and 56 days for HIV. NAT and serology test negativity on the follow-up sample, followed by test negativity on the subsequent donation, constitutes two test points beyond the reactive index donation to confirm that the donor is truly negative. This addresses Question 3.

Not include a requirement for an HIV-2 NAT because of the low frequency of HIV-2 infected donors in the U.S., less than 1 per 29 million

donations, and the low priority test manufacturers have given to HIV-2 NAT detection. Importantly, four HIV-2 infected donors detected by the Red Cross since June 1992 have been identified by current HIV antibody screening assays and the HIV Western Blot. It should be noted that in the last version of the FDA proposed algorithms, this requirement has been deleted. I just wanted to mention it for emphasis.

The algorithms should not consider reentry of donors with NAT reactive and antibody repeat reactive test results, even if unconfirmed. The yield for this category of donors is very small, approximately 105 donors annually for Red Cross, and the risks are higher for infection in donors who test reactive by two independent test methods. This addresses Question 1.

Include reentry for donors who test serologically negative but NAT falsely reactive, provided that these donors test negative for both NAT and serology on a follow-up sample and negative upon subsequent donation. Include reentry for donors who test NAT negative but seroreactive unconfirmed for HIV or HCV, provided that these donors test negative for both NAT and serology on a

follow-up sample, and negative again upon subsequent donation. That's the response to Question 2.

Regarding Question 4, for the purposes of reentry, not continue follow-up of a donor with a NAT negative test result when that donor is persistently HIV or HCV repeatedly reactive. Published data on such donors indicate that these individuals maintain persistent antibody reactivity over long periods of time.

The Red Cross believes these recommendations are prudent actions that should be taken to enhance the blood supply and the patients we serve, while at the same time allowing for reentry of donors who have tested falsely reactive by either NAT or serology. Thank you.

DR. NELSON: Thank you very much.

Questions? Sue, could you stay there a second? Ray?

QUESTIONS FOR THE COMMITTEE AND VOTES

DR. KOFF: What is your suggested interval between the follow-up sample and subsequent donation? Does it matter?

DR. STRAMER: No, I don't believe it matters, because the false positive, as every

single speaker has shown, is really an artifact of an assay contamination event. An independent sample. actually probably even taken at the same time from plasma, probably would serve the same purpose, but the reason--the intermittent viremia would be the only cause for concern, because two samples, be it a follow-up sample and then the subsequent donation going over that six-month period of time, really gives three then independent test points to assess whether the donor is truly HCV reactive or not.

DR. NELSON: Blaine, you had a comment?

DR. HOLLINGER: Yes. On the other hand, Sue, I agree that for a false positive test it doesn't matter. He could come back the next day or a couple days later. But if you're looking for a resolution of something that may be occurring over time, in terms of the education then of that donor, then the time interval I think becomes--at least to me would seem to be more important, to try to establish an actual infection or something else going on. I mean, as a clinician it would be critical to have that piece of information.

DR. STRAMER: But it's really an arbitrary time period when we take the follow-up sample,

because then if we wait the full six months for the subsequent donation, at least we would have had the index, a follow-up, and subsequent donation as three independent test measurements.

DR. HOLLINGER: Right.

DR. NELSON: Others? Okay, thanks very much.

I will tell everyone my goal. My goal is that we could vote on these four questions within the next half hour, and hopefully we'll be able to do that, because the afternoon is fairly heavy and there are reams of people that want to make statements.

So, Paul, could you--maybe we could consider Question 1. I think we have to vote on these questions separately for the two agents, HIV and hepatitis C, but I think for Question 1 we could present them together and then vote separately, because I think they are perhaps more lumpable than the other four questions.

DR. MIED: You're saying to present Questions 1 and 5?

DR. NELSON: No, no, no. I would say 1 for HIV and 1 for HCV, present together. We could vote on that, and then we could decide whether we

need to separate the other questions.

DR. MIED: Yes, we'll do that.

Question 1, which pertains to HIV reentry: Is it useful to consider reentry for donors in Group 1 with NAT positive, anti-HIV-1/2 EIA repeatedly reactive, HIV-1 Western Blot or IFA indeterminate or negative results? Again, this is the numerically small Group 1 set of donors.

DR. NELSON: Okay, discussion? Yes?

DR. FITZPATRICK: Could you do me a favor, because there's been a lot of discussion about multiplex and positive pool and resolution of indeterminates. Could you define what FDA's definition of NAT positive in this question is?

DR. MIED: A NAT positive in this case would be a positive result that was obtained on the master pool and then was found to be positive, an individual donation was found to be NAT positive.

DR. NELSON: For the committee, or those who weren't here, we voted on this last time, that if there was a pool that could not be resolved either in the subpool or particularly the individual sample, it was regarded as a contamination event.

DR. MIED: Correct.

DR. NELSON: But this one that's not a contamination event by that definition.

DR. MIED: Right. We do have a NAT positive result on an individual donation here. If a supplemental NAT test was done, if it was done, it needs to be negative to consider the donor for reentry. And we're not differentiating here, when we talk about a NAT positive individual donation, we're not differentiating between a discriminated NAT result and a non-discriminated NAT result, so we just have a NAT positive result on the individual donation.

DR. NELSON: Okay. Are there any other comments? Are we ready to vote on this one? Yes, Toby?

DR. SIMON: Did you want to vote on this one and the HCV one together, then? That's what you said earlier.

DR. NELSON: Well, why don't--yes, together, but let's do them separately and separately. Together but separately, if you know what I mean.

DR. SIMON: Yes. There seems to be little--there seems to be consensus that there's little reason to vote yes on this, from what I

heard.

DR. NELSON: Right. Okay. So a "yes" vote would mean it's useful, and a "no" vote would mean it's not useful. So how many would vote yes on this question?

[A show of hands.]

DR. NELSON: How many would vote no?

[A show of hands.]

DR. NELSON: How many would vote indeterminate or undecided?

[Laughter.]

DR. NELSON: The consumer representative?

MS. KNOWLES: No.

DR. NELSON: The industry representative?

DR. SIMON: No.

DR. NELSON: Okay.

DR. SMALLWOOD: Results of voting on Question 1: There are 15 eligible to vote on this question. There was one "yes" vote, 14 "no" votes, no abstentions. The consumer representative agreed with the "no" vote, and so did the industry representative.

DR. MIED: Question 5. Question 5 is a similar question for HCV: Is it useful to consider reentry for donors in Group 1 with NAT positive,

anti-HCV EIA repeatedly reactive, RIBA indeterminate or negative results? And here again, here is the numerically small Group 1 subset of donors that this question pertains to.

DR. NELSON: Okay. Are there any comments or discussion about this? Blaine?

DR. HOLLINGER: I sort of, just as an issue, you know, I think what has been mentioned here for many of the speakers has been the complexity of these issues. It seems just relatively simple to me, and maybe I'm wrong here but I'll throw it out for just discussion among the group, if there is some discussion, is that if you've got anything that's positive, things like this, the patient, the person comes back, the donor comes back, say three months for HIV, six months for HCV, at least, at least that time period, and it's repeated.

If they are NAT negative and antibody negative, then they could be reentered. Anything other than that, they don't. I mean, that to me is how I view most of these questions here, is anything outside of that makes it difficult for them to be brought back into the system. But if they're negative for those two, then to me that

becomes an issue that these were false positives.

DR. NELSON: Yes. It's certainly conceivable, and happens in the 12 million donors or whatever, that there could be a sample mix-up and, you know, Joe Jones is not really Joe Jones' sample, and it could be positive on both NAT and ELISA.

The other thing that I think is a little more complicated here is that with the antibody testing for hepatitis C, we've seen data that looks, the second generation and certainly the first, but no blood banks are testing with the first but there are many testing with the second generation. The third generation narrows the window period, but some data that we did in the FAC study also suggests that the third generation may be more specific, and that there may be false positives on the second generation that aren't positive on the third generation.

So I wonder if we should specify not only just "a licensed assay," but should we specify a third generation EIA or test of equivalent sensitivity? Does the FDA have any response to that suggestion?

DR. MIED: I mean, we'll certainly

consider that. The data is certainly striking on the usefulness of the EIA 3.0 relative to the EIA 2.0 when reentering donors.

DR. NELSON: Right, but yet I guess there are blood banks that are still using the--it says a licensed test, so an EIA 2.0 result would be considered equivalent in terms of the FDA regulations. Is that right, Toby?

DR. SIMON: Right. Yes, a 2.0, for those who are using the Abbott system at this point, they wouldn't have a choice. That's what they would be using. So a large part of the country would be using it until, as was commented, the new PRISM is licensed.

I was just going to comment further that in terms of your question about the sample mix-up, ordinarily the RIBA would be sent from the same sample, so if there was sample mix-up, you would expect the RIBA to be positive, in other words, if you had a true positive that you mixed up.

DR. NELSON: Yes, a good point.

DR. SIMON: So I think there's a lot to be said for Dr. Hollinger's approach, to ask the FDA, as some of the speakers have suggested, to look at simplifying some of these algorithms. But I think

given the status of where we are now and the questions we have here, I think with this question we are faced, as we were before, with very little reason to believe--it's going to be a very rare situation and I think probably not useful to have this algorithm available.

DR. NELSON: Yes. I think this is a place where the blood banking issues, in terms of adding new donors, etcetera, and the individual donor's interests are perhaps somewhat different. Any donor who tests positive for both NAT and ELISA for either HCV or HIV, he must be followed and he must be retested. But the issue is, does the blood bank have to do that, and if so, at what interval? And I don't know how the FDA deals with this, but the issues now are discussing what is a blood bank algorithm, essentially.

Yes?

MR. TABOR: Yes. I don't know whether you're going to follow up on your last comment about the EIA 3.0, but I'd like to caution you about using the term "third generation" if you do follow up on that, and just refer you to the discussion this committee had when that test was discussed a couple of years ago.

DR. NELSON: Yes, Paul?

DR. SCHMIDT: I would like to confirm that there is no hidden agenda. Is all of this optional for the blood center to do? Is this continued, that this is the way the FDA would accept but would not require people to go through all of this?

DR. MIED: It would not be required, that's true. It would remain optional.

DR. NELSON: It would be regarded as acceptable, and not to be followed up by a court summons, no.

All right. Are we ready to vote on this? So, again, a "yes" vote means that a person could be considered to be reentered; a "no" vote means no. Those voting yes?

[A show of hands.]

DR. NELSON: Okay. "No" votes?

[A show of hands.]

DR. NELSON: Uncertain? Indeterminate? No?

Consumer rep?

MS. KNOWLES: No.

DR. NELSON: Industry?

DR. SIMON: No.

DR. SMALLWOOD: Results of voting on this

question is, there is one "yes" vote, 14 "no" votes, no abstentions. Both the consumer and industry representative agreed with the "no" votes.

DR. NELSON: Well, let's move to Question 2 in the HIV algorithm. which is, should reentry be considered for donors who are NAT negative, anti-HIV-1/2 EIA repeat reactive, and Western Blot indeterminate--

DR. MIED: With viral bands.

DR. NELSON: --with viral bands present?

DR. NELSON: Yes. These are donors in Group 3. There's a subset of donors in Group 3 who are indeterminate with viral bands.

DR. NELSON: I have one question about this. We have a study at Hopkins, and there are about seven or eight centers in the United States that are trying to identify people early after infection, to try to see if they can be treated and the immune response be preserve so that they become long-term nonprogressors, and we would welcome any blood bank who finds such a person that is NAT positive prior to--I guess it doesn't--we would look at NAT positive, but this is NAT negative, so perhaps it doesn't.

But I wonder if the blood bank would ask

whether or not this person might have gone to see a physician or somebody after receiving this notice from the blood bank, and be put on antiretroviral therapy, in which case a person might be antibody positive and NAT negative. And I assume that the blood bank would take this history, but this is something of a complication in present day. With HART therapy a donor could be NAT negative and EIA positive.

Toby, is that--I mean, I assume that this is an individual--you know, that there would be a detailed interview and what have you.

DR. SIMON: Yes. I mean, the interview should certainly pick up that the individual is under medical care and is taking this type of medication, so we would not anticipate this type of donor showing up.

I think this case, this instance really goes back to what the committee considered before several years ago and voted, as I believe I'm correct, in favor of allowing reentry for Western Blot indeterminates.

DR. NELSON: Right.

DR. SIMON: And it simply says now with NAT we have even more support for that position,

because they are NAT negative. So this would seem to be to be the obvious case where we will have a pick-up, and that's your 14,000, correct, in this group? So we're talking now about a not unsubstantial number of donors in the United States who could help with the current blood shortage, as well as a group of people who are going to be saddled with some indeterminate result who don't need to be, because we have the NAT result.

DR. NELSON: Right.

DR. SIMON: So I would think it would be strongly favorable to move ahead to reenter these individuals.

DR. NELSON: And this presumes a repeat test after an interval, which was proposed to be 56 days.

DR. SIMON: Yes, you would have to go through--

DR. NELSON: And the issue is, is there a test and then six months later a donation at the time of reentry, where there is another test? That's one possible scenario.

Yes, John?

DR. BOYLE: Particularly in light of the comments by some of the consumer groups, blood

users, I think it's important before we vote on this to sort of quickly review some elements in the bidding here.

HCV and HIV we know can be transmitted by blood and blood products. The data presented here was very compelling that the risk of false negatives on NAT is quite low, but it also said that it is not zero, particularly in terms of plasma products where pooling dramatically increases the consequences of an infected unit getting into the blood. On the other hand, inactivation reduces the risk. On the other hand, GMP failures that we're told about increases it again. So if you want to follow the math, if you take apples and multiply them by oranges and divide by bananas, you've got a sense of the risk.

And against all of this, what we were told is that we're not going to retrieve 14,000 donors. What we're hearing is, relatively few of those people who would be allowed reentry are probably going to donate. The primary value, we have heard, is the reassurance of the donors who have positive results that, with follow-up, that it is either clinically not serious or we've got an error.

To put it in perspective, at the same time

we're talking about this, we also have a European deferral, and we don't know about the transmission, there is no test for it, there is a major loss of donation, and I'm curious what people are told who have spent a year in France in school. Are they told that, you know, they are at unknown and permanent risk for Jakob-Creutzfeldt disease?

So, I mean, just to put it in perspective, if you haven't guessed, I'm going to vote no, and I'll pass.

DR. NELSON: Okay. Other comments? Pat?

DR. CHARACHE: Most of this group with the indeterminate Western Blot are going to have the same pattern. Maybe it's p24 only or something of this kind. And I wonder if there should be consideration to this fact. And this reentry group, certainly if they are indeterminate, doesn't change over time, and that point was made in discussion. It's very strong evidence that it's a cross-reaction.

DR. NELSON: Right. These are not only indeterminate Western Blot but they are EIA repeat reactives.

DR. CHARACHE: Right.

DR. NELSON: You know, when we went to

doing Western Blots on everybody, we found that a lot of people have Western Blot--

DR. HOLLINGER: And along those same lines, John, I think that the fact that they are EIA repeat reactive keeps their blood from being administered.

DR. SIMON: Yes. I think that's a point. They would have to qualify on the follow-up sample, and any positive would not be used.

I'd just like to make a comment about the plasma industry, since I've gotten some attention. I think Dr. Busch's answer was essentially correct, that it's unlikely that much of the plasma industry would use the reentry protocol, but this is a company-by-company decision. If the FDA were to approve this, there would be such an option, and I think the industry stand basically is positive about having appropriate reentry protocols go forward and then being able to make its own decisions.

There are some specialized donors who have particular use, who have been reentered by the plasma industry in the past because of special needs for those individuals. But I think it becomes--this all is a very complex ethical, blood

supply, medical kind of question, but for those of us who have dealt with donors over time it has become a serious problem in terms of what we tell donors and the way we leave them, and the way the blood center or the plasma donor center appears to the community, as somebody who doesn't know what's going on, who can't seem to follow through with the testing and the information they have.

So I think this would be a step forward. I agree it's not going to be a huge step forward. I think, however, as we've heard the Red Cross, when it might now start to do this, we might begin to see, at least on the whole blood and plateletpheresis side, a fair number of donors reentered.

And just a small point that never gets-- that I don't think gets brought up in these discussions. There are donors and then there are donors. There's the donor who is the base commander or the minister of the church, who when lost may impact on that donor group. There's the O neg, CMV neg, who comes in every eight weeks for infants. There's the plateletpheresis donor who is CMV negative. So there are particular critical donors that, if they could be reentered, would be

very helpful to the blood program.

DR. NELSON: Mike?

DR. BUSCH: Just two comments. With respect to the reentry potential, and not speaking to the British and European deferral, which I think we all are very uncomfortable with, part of the issue will be, as we begin to notify these donors more reassuringly that there is a reentry option, that they were negative by NAT initially, I think many more will be interested in reentry.

Because the historical data you're hearing are donors who were deferred with a mixed message, that there's no reentry program. Then we come to them years later and say, "Do you want to be reentered?" And by then they're so ticked off. So I think we're changing the message, now that we have NAT to give these donors, and I'm optimistic the reentry will be greater.

In terms of these indeterminate bands, there has been extensive follow-up studies on donors with viral bands that has shown that they are almost universally not infected. There has been large studies that have looked at other virus cross-reactivity, at amplified reverse transcriptase, and these donors are not infected

with any other viruses. They are just nonspecific noise, and even though many will have persistent bands on Western Blot, many will revert on the EIAs, particularly as we have moved to generations of improved EIAs, and would be reenterable because we are not requiring a repeat Western Blot.

And probably the most convincing data is the study Harvey Alter did many years ago, where they went back and did Western Blots on units that had been transfused, and as Ken said, 20 percent of these donors had viral bands. None of the recipients developed any viral bands, so these are non-transmissible phenomena that have nothing to do with any virus.

DR. NELSON: My only concern, that has been addressed a little bit, is the genetic variation in recombination of HIV viruses around the world. I just came back from Russia, and they have got every conceivable virus, even those that haven't yet been described, in some populations there. And as the viruses recombine, I can see a possibility that you might get a negative NAT assay, but in a whole virus ELISA you might get positive. Now, hopefully the RIBA would also not be indeterminate but positive.

But it's a lingering concern. I think like anything, though, we have to monitor it. It hasn't happened yet. There is no data indicating that it's a current concern, but theoretically, yes.

DR. McCURDY: I'm a little bit concerned about--I'm not concerned about the Western Blot but I am concerned about the repeat reactive EIA, and if the donor comes back in eight weeks or six months or something like that and tests negative, you now have one vote positive and one vote negative, and I think I might be a little bit more comfortable if there were a third test before you reentered him.

DR. NELSON: That's an option, because we talked about 56 days and six months before reentry, and that's Question No. 3. We haven't gotten there yet.

DR. McCURDY: The other thing is that there is, I think, a considerable distinction between the use of a laboratory test to screen donors and prevent transmission of disease, and the use of a laboratory test in clinical medicine, and one's response to whether it is positive or negative and your determination as to whether the

individual is infected or not is a great deal different if you're worried about an individual donation that's going to go to patients. And I think there's ample evidence that we are not happy with 1 in 500,000 transmissions or even 1 in a million transmissions. So I think you have to distinguish between how you deal with donors. Clinical medicine has been for years replete with uncertainty.

DR. NELSON: Mary?

DR. CHAMBERLAND: A couple of things. One is, just to follow up some of John's comments and concerns, I just--I guess I wanted to make sure I understand how this vote for the Question No. 2 works and the implication of a vote.

We are being asked, for Group 3, should they be considered for reentry. And as I follow Paul down the algorithm here, if we vote yes, that they should be considered for reentry, then there's a couple of possibilities. Well, there's four possibilities. But I think the expectation is that many of these people are going to remain NAT negative, and as Mike said, you know, if they revert, their EIA reverts to negative, then in fact they will be able to be reentered.

So reentry is for sure only going to occur--we have to vote--there is a separate question, Question 4, for people who remain EIA repeat reactive, but two things: One is, if we vote for Group 3 to be considered for reentry, they're going to be tested at, even though some people are unhappy about this, the proposal on the algorithm is that there is an interval of eight weeks, a follow-up sample, and then in point of fact if they are NAT negative and EIA 1.0 and 2.0 negative, then they can be reentered, and in point of fact they would be tested a third time at the time of donation, and that would address the tiebreaker situation that Paul McCurdy raised.

I want to make sure, do I have that correct, and does that make you--would that impact on some of your earlier comments, John?

DR. BOYLE: What you've described is different than what's put up there. What appears there with the slashes would suggest an "or". If in point of fact we're talking about "ands" it obviously would increase my comfort level. It's not clear from the box or from the other that we're talking about you need both or you need either.

DR. CHAMBERLAND: Well, I think what you

have to do--what I'm finding hopefully helpful is that where Question 2 applies to on the algorithm is early up, so it's not down here. It's like should you allow these people to proceed to a follow-up test, and then if that's negative and they're eligible for reentry, they show up again for donation.

DR. MIED: That's correct. Yes, what we're talking about here is a subset of this indeterminate group--

DR. CHAMBERLAND: Right.

DR. MIED: --just with the viral bands present. We're not considering the indeterminate group as a whole, just viral bands present.

DR. CHAMBERLAND: But it's not saying that these people automatically are eligible to be reentered if they remain--if they continue to have an indeterminate Western Blot pattern. That's Question 4.

DR. FITZPATRICK: Or if they continue to be repeat reactive EIA. This is just, should they be evaluated for reentry, right?

DR. NELSON: Yes. On the follow-up sample, both the EIA and the NAT must be negative.

DR. CHAMBERLAND: Exactly.

DR. NELSON: But if the EIA is negative, they are not tested for a Western Blot.

DR. CHAMBERLAND: Exactly. Agree, agree.

DR. NELSON: But then they have to--but that's a sort of a resolution or screening assay, and then when they come in and if they elect or if they decide to reenter, they--then that unit is tested again for--

DR. CHAMBERLAND: Right. My concern was, and maybe I misunderstood John's comments and some of the consumer comments. I thought what I heard was an indication that you thought people would be eligible for reentry if they persisted in being--

DR. NELSON: EIA positive?

DR. CHAMBERLAND: --either EIA repeat reactive or have the Western--

DR. NELSON: No, if they're EIA positive--you know, probably most of these are contamination or mix-up of the original sample. That's what we think, and the data tend to show that.

DR. BOYLE: Excuse me. What I was hearing was that upon retesting, a single NAT negative would reenter you, and we heard evidence--

DR. NELSON: NAT plus EIA negative. It has to be NAT plus EIA negative.

MS. KNOWLES: Ken, can I make a comment, please?

DR. NELSON: Sure.

MS. KNOWLES: I think there are several of us here on this committee who have been here for a couple of years, and we know from past experiences that one--there has been another example with another algorithm where we requested clarification of it a few times and asked that it be reworked, and perhaps maybe that is something to consider. Certainly some of the other comments from some of the speakers, like Bianco mentioned that, maybe that's something we need to think about for the rest of this piece.

DR. NELSON: How would you revise this algorithm?

DR. BIANCO: I think that the way I would revise that, I would love to see the resolution of the questions that we have here today, I think that both FDA and us, because then we know the direction. I think that is an evolving process, and I hope that we will consider simpler systems. Even Blaine wants a simpler system.

[Laughter.]

DR. NELSON: Well, we're going to vote on

it, so depending on who wins the vote, you'll have it. Yes?

MR. RICE: I just wanted to support John's comments earlier. While I see a great need for us to resolve the issue, particularly for the donor in these cases, where in most cases if not all cases they're turning out to be healthy individuals, the thing that's of great concern to me as a user of the blood products is no so much --it's mitigated due to the inactivation processes, but what really just constantly seems to raise its head as a concern is the failure of GMP and SOPs with regards to the processing of the pooled products. And I think that comments made earlier from the audience, that's really my--you know, I'm wondering, can I truly rely on deficiencies to be corrected in a timely manner?

DR. NELSON: Marion? Oh, Jay, can you--Marion, do you want to address this issue or--

DR. KOERPER: No, let Jay go first.

DR. EPSTEIN: I want to come back to the issue of, is this really complex or not, because I think that there is an apparent complexity because we've been considering all the ways that a donor might test initially and stratifying them and

debating whether they should be eligible for reentry consideration.

But the reentry criterion is simple. All we're saying is, you come back and you have to have negative EIA, negative NAT. I mean, it doesn't get simpler than that. The logistic issues are whether it should be possible to do that on an independent sample from the original collection, or you need to have a follow-up sample after waiting a period of time, or whether you can waive that entirely and simply redonate, because if you redonate, of course you'll be screened with EIA and NAT.

Now, what the FDA is basically saying is, we'd rather have a system in which you have an off-line test before you donate another unit. And why do we say that? We say that because a large proportion of attempts at reentry will not succeed, and if you allow that to be a collection, you've collected an unsuitable unit, so we'd rather that that unit wasn't collected in the first place.

And then the second issue comes back to Paul McCurdy's point, which is that if you were to simply requalify based on a second set of tests which are negative, there is no tiebreaker. I mean, which of the two results should you believe?

And so we've really introduced into this algorithm two principles. One is that it always involves the tiebreaker, in other words, you have two negative tests following the reactive test. And the second is, you have waited long enough to have confidence in the test result, because that gets you past all the periods of time where results might be changing because of intermittent viremias, because of the seroconversion process.

So I would contend that this is in fact a simple algorithm. Now, I'm not saying the logistics are easy, but the criterion is simple, and it's simpler than many of the things that were done in the past because we're attempting to eliminate stratification based on the blot pattern; we've eliminated retesting with the blot, which added a lot of complexity, right, and also a bias because we know there's a high indeterminacy rate of the blot on uninfected people; and we've attempted to us what we felt were the minimum time intervals for retesting that could be used regardless of the test chosen.

This comes back to the HCV EIA 2.0 versus EIA 3.0 issue. Yes, if you used EIA 3.0, maybe you could have a shorter interval than six months, but

we're not mandating EIA 3.0, so we want an algorithm that will work either way.

So I would contend that this is in fact a simple algorithm, and that the appearance of complexity really is due to the fact that we've tried to stratify all the cases to figure out who might be eligible, but the algorithm itself is simple. It's a NAT test and it's an EIA.

Now, there is one other level of complexity, which is what happens if you switch tests? Because there's this notion that if you switch tests, because tests, while they may be equivalently sensitive and specific, are not identical, we want to be very, very sure that you haven't overlooked the sensitivity where one test may differ from another. And that's where all the footnotes come in saying that if you switch say EIAs, you want to be sure that the one you're coming back with is no less sensitive for HIV 1 Group O or for HIV 2. Or if you switch NAT tests, it should be no less sensitive for M variants or Group O.

So that is an added level of complexity, but operationally for the most part it's the same set of tests that are going to be used. So once

again there is the appearance of complexity, but that doesn't happen very often.

So, you know, I'm not going to pretend that the system as a whole is as simple as it might be, because as I said, the simplest thing of all would be, you simply allow the donor to redonate without prejudice, they simply get rejected each time. But we just don't think that that's the most cautious way to proceed. Nothing would be simpler than that, whereas if you got rejected once or deferred once, you know, if you were retested without prejudice, it would just mean that there was no meaningful deferral.

So if deferral is going to be meaningful, if the idea is that once deferred, you need to be extra special sure that there really is no infection in the donor, then you have to do something intermediate, and the question is what. And I contend that what's being proposed here as intermediate testing is in fact simple.

DR. NELSON: Okay. Thanks, Jay.

Marion, did you want to say something?

DR. KOERPER: Apparently this is a very simple thing, but I'm wondering if it might help to clear up some ambiguity. If you could--well, here

for instance, where you have NAT negative, slash, if you could put the word "and" HIV-1/2 EIA repeat reactive, and then a slash, put the word "and" HIV Western Blot indeterminate, because I think that's a source of some of the confusion, that some people are interpreting the slash as "or" rather than "and".

And then also on the second part, after the second, could you go back to that diagram? No, the one that has the after eight weeks what you do.

DR. MIED: Yes. I don't have that slide in this set of slides.

DR. KOERPER: Okay. Well, then, after eight weeks when you retest, there is a chart across the bottom, and it says--the one that we're concerned about is the one that says "NAT negative, anti-HIV-1/2 negative". If we could put an "and"--

DR. MIED: Yes, I do have that.

DR. KOERPER: Yes, again, where you have the NAT negative, slash, EIA negative, if you could put an "and" there.

DR. MIED: Yes.

DR. KOERPER: So it's clear that the slashes mean "and", not "or".

DR. MIED: Not "or". Yes, it means "and".

DR. NELSON: Could we vote on this? Yes, Mary?

DR. CHAMBERLAND: Paul, I have a question about Footnote No. 2. This is like a very different question. Footnote No. 2 under Group 3 there says, "If a different licensed HIV-2 EIA is negative, or if repeat reactive, an optional HIV-2 supplemental test is indeterminate or negative." Does it--is it a concern? There are currently no licensed HIV-2 supplemental tests. Is that correct?

DR. MIED: That's correct. That's correct.

DR. CHAMBERLAND: So how would this happen?

DR. MIED: What we're talking about here is qualification of the donor to be in Group 1 or Group 3. If you have an indeterminate or a negative supplemental test for HIV-1, you haven't ruled out HIV-2 infection.

DR. CHAMBERLAND: Right.

DR. MIED: So you need to at least run an EIA for HIV-2.

DR. CHAMBERLAND: Right.

DR. MIED: And what we're saying here is,

for a donor to be in Group 1 or Group 3, that HIV-2 EIA needs to be negative, or if it's repeatedly reactive and you choose to do a supplemental, that it not be positive.

DR. CHAMBERLAND: Right.

DR. MIED: Then the donor can be in--

DR. CHAMBERLAND: So people will have access to supplemental tests for HIV-2, if they're not licensed?

DR. MIED: Yes, I believe people do have access to HIV-2 supplemental.

DR. CHAMBERLAND: And that could then become a test of record, if you will?

DR. NELSON: Okay. I'm trying to get there before dinner. Could we vote on this? So a "yes" vote means that reentry should be considered, a "no" vote means reentry should not be considered. All of those voting yes on this question?

[A show of hands.]

DR. NELSON: All those voting no?

[A show of hands.]

DR. NELSON: All those abstaining?

[A show of hands.]

DR. NELSON: Consumer representative?

MS. KNOWLES: I'll vote yes, with the

qualification that the language be changed as Marion suggested.

DR. NELSON: Okay, but the understanding is that that's what it means.

MS. KNOWLES: Yes.

DR. SIMON: Yes.

DR. SMALLWOOD: Let me just reiterate that there are 15 members that are eligible to vote on this particular question. So the results of voting, Question No. 2 on HIV test results, there are 14 "yes" votes, there were no "no" votes, one abstention. Both the consumer and industry representatives agreed with the "yes" vote.

DR. NELSON: Okay. Let's move then to the same issue with hepatitis C. Are there any comments? Can we vote?

DR. MIED: That would be Question 6, Dr. Nelson?

DR. NELSON: Right.

DR. MIED: Should reentry be considered for donors who are part of Group 3, with NAT negative and anti-HCV EIA repeatedly reactive and RIBA indeterminate results? Now, we have--again, these are a subset of the Group 3 donors, and we've seen data on the prevalence of infection in these

donors.

DR. NELSON: And there is no--can there be no understanding as to what ELISA repeat reactive, which generation or which--you said multi-antigen, but that would be either 2.0 or 3.0.

DR. MIED: That's correct, multi-antigen.

DR. CHARACHE: Maybe we should also--I would appreciate a clarification of what's meant by an indeterminate Western Blot. That's not just envelope, right? Is it--

DR. NELSON: We're talking here about hepatitis C.

DR. CHARACHE: This is hepatitis C, yes. I'm sorry. I was asking another question.

DR. NELSON: And, you know, it's according to the manufacturer's instructions as to what is indeterminate, and I think they agree. All right?

All voting "yes" on this question?

[A show of hands.]

DR. NELSON: All voting "no"?

[A show of hands.]

DR. NELSON: All abstaining?

[A show of hands.]

DR. NELSON: Consumer?

MS. KNOWLES: Yes.

DR. SIMON: Yes.

DR. SMALLWOOD: Results of voting for Question No. 6 dealing with HCV test results: 13 yes votes, 1 no vote, 1 abstention. Both the consumer and industry representative agreed with the yes votes.

DR. NELSON: Okay. Now, Question No. 3 is with regard to the interval, and this is for HIV, and the FDA has proposed, instead of an open-ended question where someone may want to have 57 rather than 56 days, let's just deal with what the FDA has proposed, which is an interval for HIV of 56 days between the original positive result or original deferred and another sample that is NAT negative and ELISA negative, or to look at the question again.

Yes, David, you have a question?

DR. STRONCEK: Yes. Are we going to vote on whether or not blood centers can test on samples versus a blood donation? Jay indicated that that might be a question that we could discuss.

DR. NELSON: That's not one of the questions that we were--of the eight that we were given. But I guess, why don't we vote on this first, and then if you want, if the committee wants

to vote on the issue of using the bag or another independent sample, we can add that.

Yes, do you have a question?

DR. MITCHELL: (Inaudible.)

DR. NELSON: Okay.

DR. SIMON: I think this is the one where I was just trying to get a follow-up with Dr. Busch, where he made the distinction in the people that are EIA repeat reactive, you may need a longer time than eight weeks. So do you want to deal with that, Paul?

DR. MIED: I think I'll probably let Mike comment on the eight weeks.

DR. NELSON: And the other issue here is, and it's a question that wasn't--that isn't given, but what the FDA has proposed is 56 days for HIV, but they haven't said that the donor could be reentered at six months. Theoretically, they could be reentered at 57 days, but what they propose is an independent, another sample after an interval of--and I don't know if you want to comment on that. Can we tie those two questions together, or just separate them, or what do you want to do?

DR. MIED: That's quite correct, Dr. Nelson. As the proposal stands, we would propose

that after eight weeks a sample be taken. If both the NAT and the EIA are negative, the donor would be eligible then to give a unit, which of course would be--

DR. NELSON: But that interval is not specified, the interval during which--

DR. SIMON: Okay, so they really covered then the point, because for the EIA repeat reactive they allow continued follow-up.

DR. BUSCH: As I understand this, after eight weeks, if the alternate--if the sample is negative, the donor can come back the next day and give a unit of blood, is the way this is written.

DR. NELSON: All right.

DR. BUSCH: I guess, again, my distinction was, I think FDA has done an interesting and good thing to try to group all these different deferred donors into one bin. But as Jay was saying, that somewhat complicates your thinking.

And what I was trying to distinguish was, I think the data does support an eight-week deferral, you know, reinstatement process for donors that are EIA negative but have evidence of seroreactivity. That's what is currently allowed for p24 antigen, and all the data would support

that persons who are in that viremic pre-seroconversion phase, everyone will have seroconverted by the time eight weeks passes, so that's fine.

But by grouping this all together to also include the seroreactive NAT negatives, a concern there is that bringing those people back soon, you may end up with persistent false reactivity that will preclude them from being reenterable. It's not a safety concern.

DR. EPSTEIN: Could I comment?

DR. NELSON: Yes, Jay?

DR. EPSTEIN: I think what FDA is saying is, you have to wait a minimum of eight weeks. We're not saying that you can't elect to wait longer. In other words, if you think in your center it's prudent to wait longer in the face of EIA reactivity with negative NAT, that's perfectly reasonable. Other centers, however, may choose to simply use a different EIA. In other words, let's say you now are instituting a different generation or a different company's EIA. Well, maybe you don't have to wait. Maybe they don't have common causes of false reactivity.

DR. NELSON: And this one doesn't say two