am using Power Point instead of some slides, so if you will bear with me a minute.

Perhaps, just as a way of introduction, and I think you would probably rather I used the microphone, I am Tom Hearn from the CDC, and the area I work in is called the Division of Laboratory Systems, where I am the Deputy Director. We have for more than 10 years conducted a performance evaluation program for laboratories that do different kinds of HIV testing.

Currently there are about 1,000 laboratories, roughly, a little bit more than that, that participate in that program. These are clinical laboratories, independent laboratories, hospital laboratories, as well as laboratories who are the primary reference laboratories in their countries. So we have about 140 laboratories outside the U.S. who participate. For most of the purposes of this presentation I have tried to exclude their data, focusing only on U.S. laboratories. Where there is some international lab data included, I will point it out so that you are not misled by anything.

And how are we doing with technology here? If you want to get up and stretch, that's okay. It's been a long morning already. Mr. Chair, is it okay if they just stand?

DR. HOLLINGER: We are going to take a 15-minute break right now. It is a quarter til 11:00, and we will be

back at 11:00 and we will start and finish up with this.

[Recess.]

DR. HOLLINGER: Could we reconvene, please?

DR. SMALLWOOD: May I ask all committee members to please return to the table, please? More appropriately, to your seats. Please, may I have the attention of the audience? We are ready to reconvene.

DR. HOLLINGER: I'm sorry, Dr. Hearn. I think we will go ahead and start with your presentation, please.

DR. HEARN: Thank you, and frankly, I appreciate having had the break. It worked for me, and I believe that there was scientific evidence that others appreciated it as well.

What I want to talk to you about, really, is Western blot testing performance from a national perspective, how well do labs perform, and how do they do it. I think I would like to start off, we have kind of given you the broad message, as you know, HIV testing has really done very well, and it has done well for a lot of reasons. The technology is really very good. Labs are really committed to quality assurance, as is the Department, and in fact I think another contribution has been that we have really worked carefully to have evidence-based policy decisions which enable the outcomes to really be really very good.

So, in summary, what I am going to talk about are Western blot testing practices primarily in the United States laboratories, how much testing, how they do it, what kind of criteria are they using now, and also then give you some data about test performance. And clearly our focus in this meeting is on the analytic performance, and it is kind of interesting.

It is very important, but when you think about a laboratory test, so often we have put a lot of energy into how well the lab does its part and we don't talk much about pre-analytic considerations and post-analytic considerations, and they, particularly in clinical settings, are very important. If samples sit out too long, does it have an adverse consequence on the test result, no matter how well the laboratorian did the test? So I only bring that up to say we are not talking about that part here. We are going to focus on the lab performance part.

Most of the data, essentially all of the data that I am going to present to you this morning comes from the CDC's Model Performance Evaluation Program for HIV Testing. As I said earlier, this program has been running for more than 10 years now, incorporates about 1,000 U.S. laboratories as well as laboratories from around the world. And, again, these data only give you one more piece of the puzzle. We really heard good presentations earlier today

that laid out other important considerations, as well.

Well, why do we do the performance evaluation program? It is an important, challenging quality assurance component for laboratories, and in that respect we think it is a way to help prevent mistakes from happening. If laboratories can closely monitor how well they are doing testing by external quality assurance efforts, we think that is beneficial. They can detect problems before they become real problems.

And then, last, I think it gives us all some data. It gives us a way to monitor how testing is done and how well it is done, so that way we see that changes are occurring. We can come up with good decisions about which direction to go next.

I am not going to spend a lot of time on this. We take a lot of steps so that the data we do get from this program fairly accurately reflect day-to-day practice, day-to-day accuracy. What we do is mail out samples to laboratories and people say, fairly skeptically, say, "Well, you know, labs know that these are performance evaluation samples. Don't they do their best job?"

We instruct laboratories really to treat them routinely. This is a voluntary program. It is not a regulatory proficiency testing program. We use samples that really closely mimic exactly what they get in their

laboratories every day, and we do a lot of pretesting of the samples and the donors who are giving us the blood to make the samples, so that we have pretty good assurance of the HIV infectivity of these samples.

In terms of an epidemiologic study, the data that I am showing you today probably could be thought of as a convenience sample because they are participants in a voluntary program. Nevertheless, we think that probably more than 70 percent of all U.S. laboratories voluntarily participate in this program. The data come from two really kind of different sources.

Every two years we have mailed out a questionnaire, a fairly lengthy testing practices questionnaire, to get really good data about how labs do tests, how many tests do they do, what sorts of quality assurance practices do they have. And these data that I will show you today are from March of '99, and then we also mail out samples twice a year for evaluating performance. The data that I will share with you today are from August of '98 and January of '99.

To repeat that we mail out samples two times per year. Each laboratory will receive samples in a shipment, and these samples can be a combination of any of these. They can have strong HIV antibody reactivity, weak reactivity, negative samples, as I show here.

Well, who are the laboratories that are participating? And this is U.S. laboratories. As you can see, they are predominantly hospital laboratories, followed by independent laboratories, public health laboratories, blood bank laboratories, and a group of others which I believe includes all U.S. manufacturers. It does, I know, for EIA testing, and I believe it does for Western blot testing as well.

How much testing do these laboratories do? Clearly, Dr. Stramer showed us that the Red Cross is involved in a lot of testing, but that is one part of testing in the U.S. In fact, we have estimated that there are probably about 40 million HIV tests done a year. That would include in the blood bank setting.

If you look at the red bars, we ask labs, "Could you just tell us in a representative month, a recent representative month, about how many samples you test?" This is the kind of distribution you get, and this is for laboratories that also do Western blot testing, this distribution is. And in the white bars, you can see the distribution for how many samples a month are tested by Western blot. Just as a crude estimate, if you took midpoints and multiplied it times the frequency and then 12 months a year, you would come up with roughly about 400,000 Western blots a year by this group of labs who provided this

data.

This is the distribution of test kits used, and what I would like to tell you on this slide is, this does include the international laboratories. So the group of "other" here includes mostly kits not used in the U.S.A. and not licensed for use in the U.S.A. If in fact we focus down on the United States laboratories, the other group gets fairly small, with the users of the Epitope/Organon Teknica kit being about 38 percent; the Bio-Rad kit, about 36 percent; and the Cambridge test, about 25 percent. And I must admit, as companies change names and acquire each other, these names may be the ones that were used at the time of the survey; they may have changed slightly since then.

We then ask the laboratories, through this questionnaire process, what sort of criteria are you using? And for sake of completeness, I know we are not talking about criteria for a reactive blot here, but this is what laboratories, U.S. laboratories, tell us that they are using for the criteria for a reactive test. The top of these criteria is the criteria recommended by the CDC and the Association of Public Health Laboratories, and about 85 percent of the laboratories say they use these criteria.

This was fairly interesting, that we also asked them, what do you use for determining a non-reactive blot,

and about 70 percent say they follow the recommended practice of no bands; about 29 percent say that they use the criteria of no HIV-1 specific protein bands present. I was asked, in gathering this data, what kinds of laboratories these are, and in both groups we really find labs who self-report as all kinds of laboratories you saw on our earlier slide. And as a proportion, in fact, we find that public health labs, independent labs, hospital labs tend to be using "no bands present" preferentially.

This is just a repeat of what Paul Mied showed you this morning, with some extra words here. Up until 1999, the Association of Public Health Laboratories' recommendation for interpretation of a non-reactive Western blot had these other words at the end that is kind of an out. It says, "Laboratories with extensive experience and confidence in interpreting Western blot bands may consider a non-reactive blot to be one that contains no viral specific bands. If there is any question as to whether a band is viral or non-viral, the blot should be called indeterminate." And so up until 1999 when, as Dr. Stramer so accurately pointed out, the Association of Public Health Laboratories decided to revise the recommendation, this is what they had used.

I show this slide just to let you know that it has been a struggle, actually, to get uphill to laboratories

uniformly using criteria. It has taken a while. You heard that the MMWR was first published in 1989, specifying criteria to be used. At that time we all would admittedly know that there were a number of different criteria being proposed to use and being used. So it took a few years for laboratories to adopt these criteria, and when we follow this from participants in our program, we see that now almost 90 percent seem to be following the criteria. It did take some time to get that up to that point.

Okay. If I could switch gears a little bit, that is a little bit about testing practices. Most of you on the committee, I know, have a handout. The next four slides just are here to give you a global picture of how well labs do with the bottom line. Do they call positive HIV infected samples positive? Do they call negative HIV infected samples negative? Just to give you some sense of how that works. And, as I said earlier, they do a pretty good job.

In this slide from August 1998--and this is one of those that is everybody, this is all participants, including the national laboratories--to give you a frame of reference, because you are going to have to read the next four slides the same way, we actually had 14 people who donated the blood, the plasma, to make up the samples that went into this shipment. Every laboratory, I told you earlier, gets six samples. When they get their mail and it is a package

from CDC, they get six little vials, and in this particular event five of them, five of the samples were reactive. Of this six, some of them were weakly reactive; that is that when you run these samples as we have collected them with all the licensed kits, they did not have bands from all of the significant viral bands.

So we had 3,545 results from 701 laboratories. Of those, eight called those--eight were non-reactive. So a small percentage called a positive sample non-reactive. Again, all of the samples we used in our shipment were HIV infected samples.

When we look at Western blot testing for those samples, we had 1,302 results from 261 laboratories. Almost 90 percent called them reactive; 131, or about 10 percent, indeterminate, and this could be considered a correct answer because, as I told you, we did have weakly reactive seroconverting samples in this panel; and there were no calls of non-reactive for these positive samples.

Now if we take that same shipment and every lab would have received one negative sample, they didn't know it but they did, and there were two donors, individual donors, whose blood was divided up to make these, so for 701 labs we had 708 results. Some laboratories may be doing more than one test, evaluating a new kit, and it is perfectly okay if they give us results from more than one test, so that is why

there could be a slight difference there.

For the negative sample we had four that were called reactive. For the Western blot--and we do ask the laboratories, "Test these just like you would any other sample," so you are going, "Why do we have any Western blot test results?" Some laboratories decide to go ahead and test them anyway. Some laboratories are manufacturers or research laboratories, and they provide that information, and that is fine. So we do have some data here, but we all recognize that ordinarily negative EIA tests, the samples would not be referred on for Western blot testing. Nevertheless, we had 131 test results. Ninety-eight percent were non-reactive, and we actually had two results of indeterminate.

These data look very similar from the previous two slides. The same donors were actually used to make up the samples sent out, but they weren't sent in the same configuration, they weren't labeled in the same way. And in fact in this particular shipment, instead of each laboratory receiving five reactive samples, they received four; so when they got their six vials, they didn't know it, but they actually had four reactive samples and two non-reactive samples.

And so in this case, in this shipment we had 724 laboratories doing EIA testing, including the international

laboratories. We had five non-reactive calls for these positive samples. By Western blot, we had 1,070 results with two non-reactives, 82 indeterminates, and one of these indeterminates was for a reactive sample that in our hands and by the judgment of most everyone else who ran these samples had bands from essentially--had essentially all viral bands except for maybe the p17. It had a 24, 31, gp41, 51, 55, 66, 120/160. So to call that indeterminate is probably pretty shaky.

Here is how labs did in that same event for the negative samples. About 724 labs again. We had 1,452 results, because remember I told you when they got their box of six, they had two non-reactives in there. And we had four calls of reactivity by EIA for the negative samples. For Western blot, again you wouldn't have expected any results, but we had 258 results, one of them called reactive and four indeterminate.

So, let's shift gears. So if we just looked at the big picture, you know, people say, "Well, people shouldn't have missed anything," but a few did. But the issue that we are talking about here is, how do labs do with individual band detection? And as an epidemiologist, if you were to do a really nice 2 by 2 table, which I could have done but I put it in words, there really are these four decision outcomes when you do Western blot results.

One is, that you hope everybody does, is they get --they identify the right bands and they make the right interpretation, depending on which bands are there. They use the right interpretive criteria and they apply them correctly. The other three dot points really have to do with when labs don't come out with the right answer, how could they have done that?

And we did a study of that several years ago. We did a study of that, presented it in two different places, including the International AIDS Conference in Berlin, looking at data over several years and saying, well, when labs have problems, where do they have problems? Is it in using the criteria correctly? Is it interpreting the bands correctly? Or is it in both?

And we looked over a period of years, and as we tracked it at that time, most of the time that there was a mistake, the mistake had to do with not correctly identifying bands. You know, what they do is, they make a mistake in identifying but they apply the right criteria and get the wrong answer. That happened about twice as often as when correct bands were reported and the criteria weren't used correctly. And then very infrequently do labs do both things, have incorrect bands with incorrect interpretation.

The natural question is, does that hold today? I don't know. We would have to look at our data. I suspect

it wouldn't be widely different, but without looking I couldn't tell you for certain.

But let's look a little closer and see exactly how laboratories who arrived at the right answer, as I showed you four or five slides ago, did with identifying individual bands. And let's focus on two groups of samples, and these are for U.S. labs only, and it is from pooling the results across these two shipments.

If we look at strong positive samples, and in those two shipments we had 11 donors who by testing in our hands with all licensed kits again had p24 bands, p31, on up the line through 160, and so we had 1,296 test results; 1,295 were reactive calls, and this is for Western blot; one indeterminate result.

Then I asked the people in our group to take a look at bands that should have shown up, and we could have picked others but we picked 24, 31, 41, or 120/160. How did labs do? They should have gotten, everybody should have gotten them. They were there, they were strong. But in fact there were 48 results that did not include one of these, and so that is about 4 percent of the results.

Looking at negative samples, and there were absolutely no bands in pre-shipment by any of the commercial tests, and that includes no viral bands, we had 275 test results. Again, you wouldn't have expected to have many

test results for a Western blot. We had four indeterminate calls for these negative samples, and five reported viral specific bands. The origin of that problem we don't know. It could be carryover when they do their testing. You could imagine other reasons.

So I said, "Well, what is another way we could look at"--

DR. HOLLINGER: Dr. Hearn?

DR. HEARN: Yes?

DR. HOLLINGER: We are going to come--I am going to ask you to probably, if you could, to just pick up the most key points at the end here because we are running a little bit overtime.

DR. HEARN: Okay. I can do that.

How many different blot patterns do you get for negative samples, positive samples, weakly reactive samples? This slide says that for the two negative samples in this column, if we had the perfect world, I would have shown a 1, comma, 2. That says there had been one pattern and we would have seen it twice. In fact, for one sample we had three patterns and the other five. That is not bad.

For positive samples, for one sample we had seven different patterns observed by participants who analyzed the sample. For another sample up here, we had 29 different patterns observed. When the samples get harder, when they

actually have fewer bands, you actually have more patterns, so labs have a hard time then making fine distinctions across bands.

These are viral bands. This slide only provides further evidence of that, and to show you in our hands this is what the test results were. For this 120/160, 43 or 53 percent of the laboratories who tested it said that there was a 160. It was equivocal in our hands, not meeting criteria for positive. Here there was no 31 band; a few laboratories reported the 31, 32. The same kind of trend was shown for a different sample, a seroconverter.

The ultimate test is, how do labs do with non-viral bands. As I told you, we haven't sent out samples to our knowledge that have non-viral bands, but we give laboratories an opportunity to report all bands they see. So I did ask just yesterday, and this is very fresh, "Show me kind of some data about what labs reported."

And what we found was, non-viral bands were not detected for any samples in pre-shipment. That is, we didn't think they had any non-viral bands. For 15 of the 18 samples, however, we had some results where laboratories indicated they saw non-viral bands. The non-viral bands were infrequent for negative and weakly reactive samples, but they were fairly frequent for the positive samples, and you heard a lot this morning. You heard something about p42

and p70, but in fact this is just one sample, but for a reactive, highly reactive sample, these are all the different non-viral bands that laboratories told us they saw.

So, in summary, what would be the take-home message here? One is, I think we all agree that Western blot testing performance overall is pretty good, and that laboratories arrive at the correct interpretive results, but there is some problem with detecting individual bands and making distinctions between those bands. I think that currently interpretive criteria take into account laboratory performance capabilities, but clearly at some cost in testing specificity.

And we would agree with everyone who has already presented that reducing the number of HIV infected persons who receive indeterminate test results is important. Nevertheless, we are uncertain that the data are really available for predicting the outcomes that could be associated with making the kind of change, at least one change that has been talked about here.

And we also know that outcomes associated with changing the criteria could be different for more or less experienced laboratories, and may depend on HIV prevalence in tested populations. I didn't show data here, but we did an extensive multivariant analysis several years ago,

published it, where we looked at what kinds of things lead to good performance, better performance. And certainly having experience in high test volume was one of the criteria that said you are likely to do better.

And then, to repeat what you have already heard today, in recognition of the problem, you know that we have circulated pretty broadly a draft of the revised counseling, testing, referral guidelines where we have now stated that persons with an indeterminate test result can be told they can be retested in 30 days, and if they have a repeat indeterminate test result, counseled that they are highly unlikely to be infected.

So that is kind of where we are, and I would be glad to open it up to questions.

DR. HOLLINGER: Thank you.

Yes, Dr. Koerper?

DR. KOERPER: I am not a blood banker, so I just have a point of clarification question. These bands, and we have seen some pictures of patterns of bands, is each band read by a person visually, or is there a scanner or a reader that reads the bands? And if so, then is it confirmed by visual inspection?

DR. HEARN: To my knowledge, for routine practice, they are always read by a person. Anyone disagree?

DR. KOERPER: And then a corollary. Is there any

plan to develop some kind of scanner or reader to eliminate some of the variability that might come up by visual scanning or reading of this?

DR. HEARN: I don't have any information regarding that. If anyone else does, they should respond. Good question.

DR. HOLLINGER: Okay. Now we are going to have a session that is going to be opened up to the public hearings, and there have been several groups that have asked to respond. The first one will be Dr. Joseph, who is responding for the Association of Public Health Laboratories. And I am going to ask you to try to keep your remarks to around five minutes, please, for each group. You may come up here, if you like.

DR. JOSEPH: I can do it from here, thank you.

DR. HOLLINGER: Okay.

DR. JOSEPH: Yes. I am Dr. Joseph, Director of the Laboratories Administration of the Maryland State Department of Health and Mental Hygiene. I chair the Human Retrovirus Testing Committee, and that committee is a committee of the Association of Public Health Laboratories.

The statement that I am going to make was one that was recommended by the Human Retrovirus Committee in March of 1999 on the Western blot criteria, and approved by the board for the Association of Public Health Laboratories.

Again this year, in fact just last week the committee met again, and the attendees there reconsidered the criteria for Western blot interpretation and reaffirmed what was acted on a year earlier.

And you have heard from Dr. Stramer referring to that statement, and basically it says that only viral bands should be used in interpretation of Western blot. If there are non-viral bands only present, then it should be read as a negative or non-reactive; and that if viral banding is present but doesn't meet the criteria for positivity, it should be reported as indeterminate.

And I think you also heard from Dr. Stramer the rationale for that a year ago, and repeated again this year, is that with the presence of non-viral bands, over the period of time since 1991, there has not been a single instance where it was associated with a different subtype of HIV or a seroconversion to HIV or some other disease involved. So it is clear that if you read, reported viral bands from p24 up through p160, as indicated in the package insert, there shouldn't be difficulty.

The group also recognized the problem of the experience of individuals reading the Western blot. As in the data presented by Dr. Hearn, clearly there is a problem of training and retraining of individuals, especially those that do very few Western blots and new, those who have come

in new into this area. So it was felt that the Association ought to take on this training through their National Laboratory Training Network, and that was another recommendation from the committee last week, that it was urgent to move promptly to provide this training for the performance and interpretation of Western blot.

And the National Training Laboratory Network is a joint venture between the CDC and the Association of Public Health Laboratories, with seven regional offices across the country to cover all 50 States. We do have a meeting with at least Region 3 in this part of the country next week, to begin planning the training to be offered in this region, and then that will be exported to the other regions to perform that. We think it is very important, and some of the data that Dr. Hearn has provided might identify the groups that we really need to get to to provide the training.

And the other issue, of course, is raising the funding to do that, but we are going to be working with it. And I wanted to say that it is pretty clear to us that that training and retraining has got to occur periodically over the years, so it is an important issue.

And that is my statement for the Association of Public Health Laboratories, and I thank you for the opportunity to make that statement.

DR. HOLLINGER: Just a second, Dr. Joseph.

Dr. Chamberland?

DR. CHAMBERLAND: I have a question. Given that the Association of Public Health Laboratories made this recommendation in 1999, so I guess it was about a year ago, can you give us any information as to what proportion--and I don't know what the denominator is, I should, but I don't know how many laboratories fall into this Association of Public Health Laboratories--but can you provide us with any information as to what proportion of laboratories have changed their Western blot interpretive criteria to the non-viral bands being read as negative?

DR. JOSEPH: In public health laboratories we had this survey that was conducted, which we do each year with regard to this meeting, and I think there were 77 laboratories involved. I believe that those laboratories use the criteria of the Association, but they are all public health laboratories. I think many of them have the experience and probably would read bands that would be considered non-viral, they are probably still, for most of them, reading them as indeterminate, and until the criteria change. Maybe someone has information.

DR. HEARN: Just maybe this will be a little bit helpful. Again, what people tell you on a questionnaire is not always exactly what they do, but approximately, when I

looked at the data where labs said that they used the criteria of "no bands present," we had 48 public health laboratories respond to that question, and 39 of them said that they used the criteria "no bands present" as opposed to nine who said that they used "no viral bands present."

DR. JOSEPH: Good. Thank you.

DR. HEARN: That was in 1999.

DR. JOSEPH: Okay. Any other questions?

DR. HOLLINGER: Thank you, Dr. Joseph, Dr. Hearn.

The next person who asked to present is, I don't have a name but it is someone from Calypte. Is that right? Is there someone here from that organization or from that company? I guess not.

VOICE: Calypte is here but we did not ask to present.

DR. HOLLINGER: Oh, okay. Sorry about that.

Then Andrew Goldstein from Epitope.

MR. GOLDSTEIN: In case I get cut off for exceeding the five minutes, I would like to make one point in the way of a conclusion from what I have heard so far, and that is that it is certainly clear to me that there is a variability in the nomenclature which is being assigned to what are being called non-viral bands, or perhaps bands which in fact are viral. And partially in response to Dr. Mied's presentation, there might be the need for some

additional studies to come to some agreement on in fact what are viral and non-viral bands, because there are things like intermediate breakdown products of the HIV genome which in fact could be called non-virals by some and virals by others.

With that, let me go quickly through some points that I have here. First, Epitope manufactures two Western blots, one for serum and plasma and one for oral fluid. These products are distributed by Organon Teknica Corporation. And of course, as I think everyone knows, if you make a Western blot using viral lysates, you are going to get cellular proteins in there, and some of those that have been described in the literature are the HLA Class I and II and actin.

There are two primary non-viral bands in the Epitope Western blot, one which we call p70, which you have heard before, and the other which we call p45. Now, perhaps this is very similar to the p42 that has been described elsewhere.

We also refer to two what we call "pseudo bands" which we believe, and have some data to support, are in fact gel marks, which is the top and bottom of the polyequilamide gel which at a certain point in the process is mated to the nitrocellulose to transfer the bands, and I will show you a picture of that. And we have done some studies to show that

when you use monoclonal antibodies against gag, pol, and env gene products, you don't see at least these non-viral bands referred to here. Next overhead, please.

And I have simply two other points. Epitope's history with regard to customer complaints is that there have been six customer complaints since 1994 regarding non-viral bands on otherwise HIV negative serums with our serum blot as the cause of an indeterminate result, and with the oral fluid Western blot since its approval in 1996 there have been no complaints about non-viral bands. Next overhead.

Here is a simple graphic of where we have assigned our two non-viral bands. One is at p70, which again I think is probably shared in common with the other Western blots that have reported it, and I would suspect is the same protein although I can't tell you exactly what that is. And then p45, which resides directly above gp41, and then these two gel marks, one very close to the bottom of the strip and then the other one above gp160, right near this green reference line on top. Next overhead, please.

Here is an actual photograph of these two bands. What we did in this particular study was to take a very strongly non-viral HIV negative serum and then both run it separately with the negative control in our product, and then to combine it with both our high positive and low

positive controls to show you exactly where these bands reside. And in the case of the high positive, you can see the p45 directly above the gp41 in both the high positive and low positive, and the p70 which resides about 2 millimeters above the p66. Next overhead, please.

In the next few overheads, these are simply taken from various clinical studies we have done. These are comparing the oral fluid Western blot, which is the purple band and white background, with the serum Western blot, and in these instances you can see the occasional p45 here and here, and here is the gel mark. That is fairly weak, but on top you can see what appears to be a band but in fact we believe is the edge of the gel, and of course that is well above the gp160 shown in the control. Next overhead.

And here is another example. There is the p45 here, here and here, and occasionally you will see a blood sample where both the p70 and the p45 will appear in the same sample. Next overhead, please.

And once again in this overhead of what we called noisy negative samples--we actually look for these as a way to evaluate our blots on an ongoing basis--there is that p45 again, which we think is the actin band. Here are some examples of the lower gel mark, and there is the upper one there, again well above the gp160. And then also, just FYI, these are some p24 indeterminates which appeared i these

noisy specimens.

And then finally this is a picture of a study done with monoclonal antibodies against gag, pol and env, and I apologize for the weakness and the fact that they are not terribly visible. But if you look at strip number four in each of these sets, you can see that in the case of the anti-gag there is reaction with p24; the env is reacting with the 160/120; and the reverse transcriptase, with the 51 and the 66; and then we pooled them all. In all cases and in many studies, we were never able to visualize either the p70 or the p45 with these and other monoclonal antibodies.

This is just to show you that if you do a literature search, there have been many studies done by investigators on the presence of non-viral bands and indeterminate blots in general. I particularly call your attention to reference number six, Connie Celum et al, where they did a rather extensive study back in the early '90s on the effects of indeterminate Western blots, especially with regard to patient anxiety. The next, please.

And this is a page from our product insert for our serum Western blot, and here I am simply pointing out the frequency of the indeterminate Western blots which were found in our clinical studies, with a 16.2 percent indeterminate in the EIA from repeat reactives in the low risk population, 9.8 percent in the EIA negatives. But in

the high risk population, as I think many people have observed, when you look at the EIA negatives, in fact you see a rather high incidence, in this case 16.9 percent, of non-viral bands showing up on high risk individuals, which we believe at least in part is a function of other aspects of their health and HIV infection. And the final overhead.

The conclusions that I would like to leave you with this morning is, first, that the scientific literature demonstrates that nearly all indeterminate Western blots due to non-cardinal bands are not indicative of HIV-1 infection. At least in the Epitope Western blot, two non-viral bands, p45 and p70, account for most of the non-viral indeterminate Western blot interpretations. And these two bands we believe are readily distinguishable from the cardinal viral bands, 160/120, gp41, and p24, which are the hallmark bands for determining whether a Western blot is positive.

And then, finally, it is our opinion that proper interpretation of non-viral bands in HIV-1 Western blots can be ensured by adequate product inserts that explain the phenomenon; perhaps the use of electronic media such as CDs, videotapes, and information manufacturers' web sites; proper training, including independent instructional programs, and an example of that is the CDC Distance Learning Program; and then, as you heard before, the Model Performance Evaluation Program provided by the CDC; and then finally the use of

ongoing training programs by the manufacturers.

So thank you very much for your time, and I will entertain any questions.

DR. HOLLINGER: Yes? Questions?

DR. CHAMBERLAND: I just have a question about your last slide there, ongoing manufacturing training programs. What currently--I guess you can only speak to your organization--but what currently do manufacturers or your firm do, and how do--do they in any way evaluate a client's proficiency at doing their--using their test kit, and particularly their ability to distinguish the non-viral bands?

MR. GOLDSTEIN: Well, what I can tell you is that we work very closely with Organon Teknica, who provides the technical service to the laboratories who use our product. We carefully monitor customer complaints, and at times we do see examples when they are concerned about the non-viral bands, and what we try to do is to help them to understand what these bands probably represent, although we do always refer them back to the product insert, to follow what that has to say about interpretation. So I guess it is a matter of watching customer complaints and then working closely with our distributor to help people understand indeterminate blots.

DR. HOLLINGER: Okay. Thank you.

MR. GOLDSTEIN: Thank you.

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

DR. KATZ: It is odd to come to the Blood Products Advisory Committee and finally realize that there is nobody left on the committee that was on when I was on. Somebody is getting older.

For those members of the committee who are less familiar with blood banking, I would like to begin by saying the AABB is a professional society for 9,000 individuals and 22,000 institutions that include community blood centers, the Red Cross, hospital transfusion services, and individuals responsible for collecting and processing almost all the blood in the U.S. blood supply. Our highest priority has been to maintain and enhance the safety and availability of the nation's blood supply.

We are grateful for the attention of FDA and the Blood Products Advisory Committee on this issue. You have heard today data drawn from large numbers of blood donors that are a testament to the ability of our donor history screening methods, in concert with high sensitivity screening assays, to protect the blood supply from HIV infectious donors.

The consequence of the extraordinary sensitivity of these in vitro diagnostics, when applied to a population

these patterns should be counseled that they are not infected. They should be reenterable according to already accepted reentry algorithms and any new ones that come down the line, when subsequent testing at appropriate intervals is negative. No decrement in blood safety will result, and our effort to reassure these donors will be reinforced by our acceptance of their badly needed gift.

While the impact on the total blood supply may not be operationally significant, our credibility with this subset of our donors will improve. It is important that similar advantages will accrue to the many clinically oriented HIV testing services around the country, and while I have focused on the blood sector, if anybody wants to talk about my HIV clinic or my STD clinic where we do a lot of this, I will be glad to do so afterwards.

The excellent beginning that discounting non-viral bands will represent should be a preface for considering similar approaches to other clearly non-specific Western blot patterns, for example, isolated p24 reactivity. In the blood donor setting, seroconverting donors with indeterminate blots, as we have heard from Drs. Busch and Stramer, universally have positive NAT testing even in the minipools we are using currently.

An enormous amount of historical experience, and now almost a full year of NAT data obtained under IND,

informs us that indeterminate immunoblot patterns, in the absence of full seroconversion in a very short time frame, do not represent HIV or other pathogenic retroviral infections. Roger Dodd says "non-viral" means just that.

If the data we have heard from Dr. Stramer at the Red Cross are generalizable, there may be as many as 5,000 blood donors annually in the United States with indeterminate tests being stigmatized by our inability to plainly state that their results are medically irrelevant. The FDA should start considering the use of nucleic acid amplification testing and repeat serologic testing to address the distressing mixed messages we are currently compelled to deliver. Thank you.

DR. HOLLINGER: Thank you.

Any questions?

[No response.]

DR. HOLLINGER: If not, then the final person who has asked to speak today is Celso Bianco, representing America's Blood Centers.

DR. BIANCO: First I want to thank you for the opportunity to present before the Blood Products Advisory Committee. My name is Celso Bianco. I am the President of America's Blood Centers. That is an association of 73 community-based, not-for-profit independent blood centers that collect about half of the blood supply in the country.

We talked a lot about the technology, and I want to reexpress your concern that actually Lou Katz expressed very eloquently about volunteer blood donors. That is a rare species that is on the verge of extinction, and when we notify donors of false positive results--they are rather frequent because our population is essentially negative--we are giving a message not only to them. We are giving not only to the 5,000, but we are giving a message to their families, we are giving a message to donor groups, and there is a tremendous amplifying effect that actually is one of the reasons for the mistrust that the public has on the blood collection and blood collecting system.

They actually, donors have told me, more than one occasion, "We cannot make decisions. Either I am positive or I am negative. What are you trying to tell me?" Actually, we recognize this even with tests that are licensed. For instance, there is a fluorescence assay for confirmation of HIV--or a supplemental test, Dr. Mied, I'm sorry--that on the basis of fluorescence you call a cell fluorescent or not fluorescent, positive or negative, and we suppress the indeterminate in our brains.

On these days in which we have nucleic acid amplification, in which we have an extremely important autoassay that is timed to seroconversion, and with the amount of evidence that we have that within 30 days an

individual will have seroconverted or not, we should eliminate the interpretation of non-viral bands from the indeterminate category. I think that Dr. Dodd is correct in saying that non-viral bands are just that. I just think that there is a corollary to that, is that non-viral bands are not transmissible.

And, finally, I would like to state that despite all the pressure that we have had to come to make the blood supply as safe as it is today, extremely safe, we cannot consider treating our donors as raw materials for the manufacture of pharmaceuticals. I think that we have to respect them, and this is a wonderful step in that direction. Thank you.

DR. HOLLINGER: Thank you, Celso.

Who is this Dr. Dodd that everybody talks about here? He should stand up so we can--

[Laughter.]

DR. HOLLINGER: This concludes at least the formal presentation for the open public hearing. Is there anybody else who would like to have anything to say from the public?

Dr. Alter? Okay.

DR. ALTER: Thank you, Blaine, for that enthusiastic endorsement. I have another one of my simplistic solutions here. It seems to me that we have used the Western blot as the gold standard for an EIA reactive

result, and we have known since 1985 that this was really a fool's gold standard; that 20 percent of normal people will give an indeterminate blot, even if they are EIA negatives. This is a very, very bad gold standard.

And we have evolved to the point where we have a real gold standard now in RNA testing, so I would propose that we don't just say we aren't going to count non-viral bands; I would say we move, we drop the Western blot, and we move to using RNA testing as the back-up for an EIA. We have seen beautiful data from Sue that the RNA test is always positive when the Western blot is positive, and is not positive when the Western blot is indeterminate or negative. It is very close to a true gold standard.

And if you don't want to be that radical at this point to totally drop the Western blot, what you could then do is that when one gets an indeterminate Western blot, that it is reflexed to individual PCR or TNA, whatever amplification you are using. And it is not reported as a Western blot indeterminate, it is reported as a combination of the two, and if the RNA test is negative, the donor is negative.

DR. HOLLINGER: Thank you, Harvey.

Yes, Dr. McCurdy? Is this a comment you want to make to Harvey before we get started on our deliberations?

DR. McCURDY: Well, it sort of relates to what

Harvey said but a number of other people said. First place, I believe in NAT tests, and I think they are likely to be a better gold standard than anything else. The question I have is, with the numbers that we have available now, what are the confidence limits that what is being said that is a negative NAT is going to be a non-infectious unit? What are the confidence limits of that statement?

DR. ALTER: I have unlimited confidence.

DR. McCURDY: No limit.

DR. HOLLINGER: Just before we do, because we want to get into the committee, is there anyone else in the--yes? Dr. Busch?

DR. BUSCH: I just wanted to make one comment. The data we saw from CDC on wide-scale proficiency testing, that suggested that there is a lot of poor reproducibility or accuracy of interpretation, I want to just point out that these Western blots, one is, we are dealing with multiple manufacturers that have highly discordant band patterns, so the CDC says it is negative but I don't know whether they actually validated it as "negative" on all these blots.

But the other is, each of these Western blot kits is a completely distinct viral lysate prep transferred to a piece of paper, and there is enormous strip-to-strip, lot-to-lot variability. So you can take a single sample and test it over time, and it will give you patterns and then

they will disappear because these kits are extremely inconsistent over time, especially in terms of these non-viral band contaminants.

DR. HOLLINGER: Thank you, Mike.

Yes, Dr. Tuazon?

DR. TUAZON: May I just make a comment, too? I completely agree with Dr. Alter. As a clinical infectious disease practitioner, I don't think we have used the Western blot in the last couple of years, since the availability of the PCR RNA, in the diagnosis and follow-up of our patients.

DR. HOLLINGER: Yes? Please state your name.

MR. KAY: Yes. I am John Kay from Oragon Teknica. And over the years as we have pushed these assays, I am going to talk about ELISA for just a minute, because if you push an ELISA assay to its ultimate, there is a very fine line between a specificity of 99.95 or greater and 99.8. 99.8 gives a lot of reactivity in an ELISA assay, and we have confused that with sensitivity, and because of that we have thrown a tremendous amount of noise at the Western blot system that higher specificity tests wouldn't send there.

So I think we need to consider the NAT testing thing on the other side. Where you now have a very high specificity on that side, we ought to look for a high specificity on the antibody side and preserve both the donors and the recipients. Maybe it is time to face that

issue.

DR. HOLLINGER: Anyone else from the public?

[No response.]

DR. HOLLINGER: If not, I am going to close the public hearing and we will open up the committee discussion on this topic. I think, before we do, let's have the questions at least once again presented, so we know what we are going to deal with here today. So if we could have just the questions run by again, and then we will open it up for discussion.

DR. MIED: Should FDA permit indeterminate blots with only non-viral bands to be interpreted as negative?

DR. HOLLINGER: Let's go ahead and deal with this question here. Who would like to start? Dr. Schmidt?

DR. SCHMIDT: Dr. Alter has brought up something which has never happened in the history of mankind. We have never dropped a test applied to blood or substituted it with anything else. So my question really is, since we were asked specific things to consider by the FDA, are we allowed to consider the NAT situation in our committee discussions?

DR. HOLLINGER: I think we need to open it up. I mean I think we need to consider everything, at least from my standpoint. Okay? So I think we should.

But I think Dr. McCurdy has brought up some important questions about, if you are going to deal with NAT

testing, how many false negatives are there in the group, if any? And, secondly, if you have got problems at laboratories who are out there doing all these tests with the several assays that are out there right now, as presented by Dr. Hearn, with abnormalities, how much do you think you are going to find in laboratories who are doing Nucleic Acid Testing in terms of responses? How many false negatives and false positives are you going to find out there in these labs? We are now talking about real good laboratories that are doing them, but there will probably be a lot of other laboratories that are doing them, perhaps other laboratories doing them, too, and what are the issues there? Yes, Dr. Simon?

DR. SIMON: It seems to me that on question number one, that we have had overwhelming evidence to say yes, basically, that indeterminate blots with only non-viral bands could be interpreted as negative. This would improve our message to donors, give us some degree of additional units through the reentry process, and particularly allow us to reenter certain particular donors like the O neg, CMV negative, or high titer specialty donor, that sort of thing.

It seems to me the NAT discussion relates to the question to come, in terms of what additional studies we would ask the FDA to do. I don't think we could deal with it today because it is a non-licensed test and the full data

aren't there, but certainly to pursue that from an investigative point of view as to how the NAT could substitute for Western blot and be more definitive, I think that would be very useful in the future. But this would be a step that we could take, I think, that would be very helpful to donors and would help a little bit with supply.

DR. HOLLINGER: Dr. Ng?

DR. NG: I would like to speak from the diagnostic clinical laboratory perspective, since your recommendations here for the blood donors will apply across the board.

As a clinical laboratorian, I feel very strongly that the results we generate should be the truth. And because you have reactivity with bands, you do not have a true negative blot, so I actually favor Dr. Mied's second compromise which is on the next slide, that the report be indeterminate with a distinction between viral versus non-viral bands, and you leave it to the individual clinician to decide how to interpret that.

I would like to bring up two other points which relate to NAT. Dr. Simon briefly referred to the big problem we have in clinical labs. It is not FDA-approved for diagnosis, so any test we do which is used for a diagnostic purpose runs into problems with our ability to get reimbursement and, more importantly, to be investigated by the OIG for fraud if in fact we do bill for that purpose.

I do want to comment that the use of NAT testing--the third and final point--in the acute diagnostic setting, we do not know, in our limited studies that we have done at San Francisco General, we do not know what the false negative rate is. We do know the false positive rate ranges between .5 to 3 percent, and a certain subset of these indeterminate Western blots, if you are going to use that in your stratification, will certainly fall into this false positive group. The viral load ranges, just FYI, tend to be under 10,000.

DR. HOLLINGER: Dr. Chamberland? Oh, excuse me, Dr. Boyle. I have been ignoring you. Sorry.

DR. BOYLE: That's all right. I just need to understand one think, and I want to sort of follow up on what Marion did, in the interpretation of a Western blot, we now think it is done by a human, but is it done by one person or does it require agreement between two readers?

DR. HOLLINGER: I imagine it probably doesn't require agreement between two readers, but somebody who is working in the laboratories--maybe you could tell us, Susan, in the American Red Cross, do you require it to be confirmed by another person or not?

DR. STRAMER: All supplemental test results, whether they are the HIV-1 Western blot or any test that we do, has to be concurred by a second individual. If there is

any disagreement, a third person resolves the disagreement. But again, I can only speak for Red Cross.

DR. HOLLINGER: Does anyone else have--yes, Celso?

DR. BIANCO: Yes, that is a standard that we also have at New York Blood Center, and actually they will enter it into a software that will compare the two readings and flag the result for review, supervisory review.

DR. HOLLINGER: Thank you. So it looks like, John, that most of them are using two readers, at least a confirmatory, another confirmatory test.

Yes, Dr. Chamberland?

DR. CHAMBERLAND: Just to follow up on that immediate discussion, I am not sure, does anybody have any information about the concurrence of multiple readers for indeterminate Western blots in non-blood bank testing settings? For example, in the public health laboratory network, are multiple readers required as they are in the blood banking situation? CDC? Tom?

DR. HEARN: Mary, I can't directly answer that question, but this thing about how many readers look at a Western blot, when we ask laboratories how many people are doing the testing, a little bit less than 40 percent--I can't remember--it was 35 percent of the labs, roughly, had two or less people doing testing, and this is all laboratories.

So please don't assume that in every laboratory there are three or more people involved in interpretation. I don't know how many people are. It could be that the analyst, the tech, reads it, and the supervisor, technical supervisor, may then review it, but I can't tell you what the actual number is. But I do know that at many laboratories there are not three or four people who do testing, altogether.

DR. HOLLINGER: And I think not only that, but as a person is in the laboratory, they have various degrees of expertise and skills. Obviously if somebody starts out as a new job, they are not going to be quite the same as a person who has been around looking at Western blots or bands for many years. So that always creates somewhat of a problem, a potential problem, is you have new people come in and are learning how to read these finite bands.

Yes, Dr. Chamberland?

DR. CHAMBERLAND: Yes. I guess I wanted to lay out on the table a different perspective from Dr. Simon's, which is, I don't really think that the question that has been posed to the committee really turns on do non-viral bands represent anything other than what Roger Dodd has said is not HIV infection. I think that there really is a substantial body of information and data to suggest that non-viral bands are just that.

I think the question really turns more on issues of proficiency and the expansion of this question to a non-blood donation testing arena. I think the data presented by Sue and by ABC and others, I mean I think we have a tremendous amount of confidence that these are really good labs with really good QA in place. They have the advantage of dealing with large volumes of test materials, and there is also the safety net of NAT that is in place.

And while I agree with Dr. Ng's comments that as a clinician in a diagnostic setting, one-on-one, I would certainly like to see NAT done as additional follow-up testing to try and sort through these uncertain cases, there is no guarantee in the wider arena of diagnostic testing and public clinics and whatever, that the NAT is going to be available as it is now systematically, really part of the algorithm of testing for blood donations.

And, furthermore, we know that the blood banks are testing low prevalence populations. That is part of the problem, is because they are so low prevalence, the issue that you end up dealing with are these individuals with false positives. And we have seen data that has been presented, it was summarized in the statement that Paul Mied made, that the committee got in writing, information about what proportion of all indeterminate Western blots have non-viral bands, and since indeterminates represent about 45

percent of all repeat reactive samples, 67 percent of these are non-viral bands only.

We haven't seen comparable data presented for other venues, the anonymous testing and counseling sites, the STD clinics, drug treatment centers, where patients clearly in higher risk populations are presenting for testing. And I have to say in that kind of a setting, with a patient, individual patients with high-risk behaviors who have EIA repeat reactives in duplicate and a Western blot that is being read out as non-viral bands, I think on a one-on-one, my confidence in saying "Non-viral bands only, it's negative, you're not infected," I really think that I would want to have the safety net of an opportunity to retest that patient.

So I think that is what I would bring out in the discussion here, that I think we have to think beyond just the blood bank setting. And it is kind of an unusual situation that the BPAC is being asked to address something that goes just beyond the blood bank testing arena.

DR. HOLLINGER: Yes, I think those are really good points. I think you see it enough in the clinical arena. I think donors are--this is going to be a little broader here. And I don't think there is any question in my mind that when you see patients who come in, or you see laboratory results come in, they are interpreted very erroneously by different

individuals, what these mean, what it means.

And I think there is some benefit to not only saying that there are some bands here and they are probably non-viral, if they are non-viral, the patient is not infected, but the patient really needs to have something else. And a Nucleic Acid Test of some sort would be very good information to have, to be able to be very secure in your being able to tell that patient that "You're not infected." I have no problem with that, at that juncture saying "Look, you've got, I mean it looks like these are non-viral bands here, and the NAT testing is negative. I can assure you that you're not infected."

Yes, Mr. Rice?

MR. RICE: The question we have before us now leads me to the corollary that Dr. Alter presented, using the NAT as the confirmatory test. If we were to yield to question one and permit question one to be a yes, and then eventually evolve into criteria which makes NAT an approvable secondary confirmatory test, how willing would industry be to basically, again basically take a back step--they have been able to operate under the situation proposed in question one--and now reintroduce this confirmatory test at a later date? I think that probably industry would be much less willing to go back than forward.

DR. HOLLINGER: Yes, Dr. Katz?

DR. KATZ: I share Mary Chamberland's concerns, because I am schizophrenic and actually take care of patients, but I would point out that high risk individuals seeking testing are almost universally candidates for retesting in the time frame of seroconversion, so the appropriate counseling message to high risk people is not much altered by a change in Western blot interpretations.

DR. HOLLINGER: Thank you, Louis.

Yes, Dr. Schmidt?

DR. SCHMIDT: Is the FDA asking us to consider the question in relation to testing blood donors, blood products, or the entire clinical laboratory field?

DR. HOLLINGER: I think it is just limited to blood donors but, Jay, do you want to comment about it? But it will have ramifications elsewhere

DR. EPSTEIN: No, actually it is the other way around, Blaine. We have not separated interpretations for blood donor testing from general medical testing, and we do have within our regulatory purview the oversight of all HIV or AIDS-related tests in the blood program. So you are being asked a question pertinent to the use of these tests in all medical settings, not just the donor setting. Now, there are some particular issues that have been brought forward about the donor setting because of the low prevalence population, but this is general.

DR. HOLLINGER: You know, if you read the statement correctly, if everything is true with the statement, it says "Should FDA permit indeterminate blots with only non-viral bands," and we are not talking about is it falsely non-viral or is it true, then the statement is pretty clear. I don't think anybody on this committee is going to have, I would think, from what I have listened to, I don't hear much dissention that you could call those negative. So I think that is--I mean, if you just take the statement at face value, it seems to be pretty straightforward with this issue here.

Yes, John?

DR. BOYLE: But, Blaine, I think part of the question is that, are you setting the standard at the level of the good laboratory, or are you setting the standard for the person who has been described as the new person, only one in the laboratory, doesn't see many of these things come through, and do you want it to have it's just blank is okay, or you have to make some interpretive decisions?

DR. HOLLINGER: Yes, I think probably you need an algorithm that follows a little bit further along here, and I think that is what some of us have mentioned, about some sort of another test that would help in that way.

Sue?

DR. STRAMER: I just want to say, to those

laboratories who aren't proficient in Western blot testing, or those individuals who aren't proficient, they shouldn't be reporting. The issue is greater than just not reporting p70's. It is perhaps not reporting the confirmed positive. So, I mean, p70's are really a very minor part of the problem, and in a high risk population, most of what you see on a Western blot is going to be a confirmed positive. You are not going to have these issues with p70's or p5's on mostly negative strips. In a high risk population or a public health laboratory, it is much easier and it is much more clear-cut.

And I also would ask the question, how many public health laboratories are truly reporting out p70's? I mean, you know, they are really--I know Dr. Hearn's surveys, but I think the practical sense of it, even though 39 out of 45 or whatever the number was said they are reporting out, it is the way the question is written. But I would guarantee you that if you went into a public health laboratory and said, "How many of you would report this out as a gp120 or 160, when you see a band way above that?" they would all tell you they are not.

When I presented our data at the American Public Health Laboratories Association, I know after I told them what our criteria are, that we are reading background and we are reading p3's and we have to make up molecular weights

for garbage we see on Western blots, they have all told me that I am nuts, and how in the world would the Red Cross be doing this? How can, as a public health laboratory, we be giving out these kinds of messages to individuals? That is bad public health.

But I have to refer to the fact, this is what is defined in the package insert. Truth or non-truth doesn't matter. It only matters what is written in black and white on the package insert. So that is why this change, albeit for anywhere from 14 percent to greater than 70 percent of non-viral band indeterminates, depending on the manufacturer, would actually be improving the public health message that we give to blood donors and other individuals.

DR. HOLLINGER: Thank you, Sue. Yes, I mean if you really look at all those tests that were presented, I think Dr. Mied also showed some data there, you can almost select the test you want. If it is positive in one, you get a p7, p5, and another test doesn't usually pick up p7, p5, you could use that assay and find this person now negative for all bands. I mean, I think that could be pretty clear. You could almost select your assay after that.

If there are no other--yes?

DR. CHAMBERLAND: I guess I just wanted to comment that, I think as most people know, I am not a laboratorian, but when CDC became aware that this agenda item was going to

be placed before the BPAC, it engendered a fair amount of discussion among the Division of HIV Laboratories at CDC. I mean, I think my understanding of those discussions is that most people would certainly not quibble that if labs are going to get an EIA positive, Western blot positive, the chance that they would be told they are negative on a Western blot, everybody agreed was fairly unlikely.

I think the concern more turned a little, as I understood it, turned on individuals who were EIA positive, Western blot indeterminate, who might be in a seroconverting window period. And as I understand it, yes, the vast majority of those people exhibit a very typical sort of banding pattern as they are seroconverting.

But again, and I have to rely on my laboratory colleagues, I understand that there are instances in which there could be things like a solitary, you know, p65 showing up. Well, would some labs think that was a 70 or something like that? Again, I am raising questions that my colleagues have brought to me.

And the other piece of information to put out on the table is that the Public Health Service is fairly far along in developing a new counseling and testing recommendation and report that has, I guess, been some months in the preparation. And I understand that there is a lot of unhappiness that the current recommendations really,

from that '89 MMWR, suggest that testing, follow-up testing has to be done within a six-month period, and that is very difficult, for individuals to be carried along for six months, told that they might be, you know, indeterminate, "We're not sure of your status."

And that given the evolution of serologic testing over the last decade or so, that now the plan, as I think Tom and Paul Mied indicated, is that the guidance that has been drafted is now moving toward a recommendation that individuals who test indeterminate be retested one month later, and if that Western blot pattern has not changed or evolved, that they be told that this really can be read as an individual not being infected.

And I guess I throw that out as an alternative approach to this thorny problem of how do you deal with individuals who are indeterminate and the kinds of counseling messages you give them, that people should be aware that there is a move afoot to really change the counseling message to something that I think everybody would agree is much more reasonable.

DR. HOLLINGER: Okay. Yes, Dr. Epstein

DR. EPSTEIN: Two comments. First of all, regarding NAT testing, the question whether the Public Health Service should move toward recommending NAT in lieu of Western blot as the supplemental test of choice really is

a question for another day. We understand that, but you are still left with the issue of how do you interpret a Western blot, and the Western blot is not likely to vanish overnight. So I think that, you know, with all consideration of the emerging value of NAT, we shouldn't confound the issue. There is still the question of how to interpret the blot. It should stand in its own right. It can't be interpreted one way or the other based on some other test result.

Having said that, the counseling message should take advantage of all available information, and there is nothing that FDA has ever said that would indicate that if you have additional data, you shouldn't use it. So, you know, I am all for incorporating results of NAT in interpretation messages--I'm sorry, in counseling messages. We have allowed that in the IND studies, and I would look forward to that being the case when there are approved products.

The second point that I would like to make is that what this issue is really about is the likelihood that indeterminate patterns in HIV infected individuals could be confounded with non-viral band only blot patterns. That is the error we are trying to prevent, if it is real, and that is what you are really being asked to think about.

I think that, as has been said, there is abundant

scientific data that if you were sure that it was only non-viral blots, then you are fairly sure that it has no known medical significance and is certainly not related to HIV. That is really not the hard part.

The hard part, again, is whether indeterminate patterns in persons with HIV infection could be confounded as non-viral only band blots. And we have seen data to suggest that they could, but it is only indirect data. It is based on recognizing a very high degree of variability in band assignment in band assignment in laboratories in the CDC-conducted proficiency studies, but unfortunately those data are not broken down by which bands were misinterpreted.

So let me ask a question that perhaps can be answered by some of the large testing laboratories present, represented in this room. If indeed the early seroconverter always shows p24, and if the reading of the p24 band is highly proficient, then the chance for those blots to be misinterpreted as non-viral is in fact very, very low.

See, the problem is that the real risk here needs to be assessed by understanding how proficient the readings are, band by band, and we don't actually have those data, at least not what we were able to gather for the committee. So I would ask if anyone can comment specifically about the ready distinction of seroconverter band patterns versus non-viral band patterns and comment on a band-specific

proficiency.

DR. BIANCO: Jay, Celso Bianco, New York Blood Center. I don't think that any lab with average experience will ever miss a p24 band. It is so clear, it is so evident, and that is, as we see in the training of our people and all that, is never a major issue. I just want to make another comment. And so I don't think that you can confuse easily a non-viral band, or miss it, for a band that is of importance.

DR. HOLLINGER: Celso, I think the issue was, if I understand what Jay said, the issue was, in a seroconversion, in a seroconversion, does the p24 always appear first? I think that was, if I am not mistaken, Jay, is that correct?

DR. BIANCO: No, you may have blots on occasion in which you have--it is always there, but in old blots you would have on occasion individuals that would have all the envelope bands before--

DR. HOLLINGER: But will the p24 be there? Do you know. Yes, Sue?

DR. STRAMER: I think Mike will address the same point. In studies we have done at the Red Cross in collaboration with REDS, and studies that REDS has done in collaboration with REDS, even though the criteria now for positivity--and hopefully this will answer Jay's question--

the criteria for positivity today are any two of the following: p24, gp41, or p120/160, actually in all the samples we have looked at since the beginning of combination testing in blood donors, including the Red Cross, in all of our samples since 1992 we have never found a seroconverting sample that didn't have p24.

All of the ones that are allowed to be positive based on envelope only, none, zero, have been RNA positive. A subset of those include follow-up, showing that those donors are not positive on follow-up, but clearly the ones that we have experienced since 1992, positives in our hands have always exhibited p24. Generally, the p24 is a very strong band, just like if you took a Sharpie on a piece of paper and drew the band. p24's cannot be confused with any non-viral band, at least in our own experience.

And I just want to say one thing to address Mary's comment about p65. Tell your laboratorians at CDC who say that, they need to get out in the real world. p65 is not the first band that shows up on seroconversion. It is always the same pattern. HIV seroconversion, whether it is timed by RNA concentration or by patterns on Western blots, is a completely reproducible phenomenon, and it is usually--well, always starting with p24 and high molecular weight glycoprotein.

DR. HOLLINGER: Thank you, Sue.

Yes, Dr. Hearn?

DR. STRAMER: And actually that is true. Roger Dodd is making another good point, reminding me.

DR. HOLLINGER: Can we have Roger Dodd make these points on his own?

[Laughter.]

DR. HOLLINGER: This is a puppet show here.

DR. STRAMER: The cutoff criteria, cutoff criteria for the blot is the weak positive control, that actually you are required to read p24 to interpret the blot as valid, the whole strip. That is your cutoff criteria, that is your calibrator that you have, p24 and gp120/160. If you don't have those in your batch of blots, the batch of blots are invalid, so you have to be able to read those blots, your weak positive control, to continue to read the rest of the strip set.

DR. HOLLINGER: Dr. Hearn?

DR. HEARN: Yes. Regarding that last issue, I believe that is test specific, depending on which manufacturer's test you use. It is not every test uses the p24.

But Dr. Epstein raised the question, does anybody know how labs do with individual bands, particularly the p24? I actually had a couple of slides that we raced through at the end, because we did have five seroconverters,

and in fact, the news is labs do pretty good.

There were occasional misses of the p24. But, as I also said in the beginning, these data don't answer everyone's question because it doesn't say anything about non-viral bands, you know, would a lab have confused a p24 with a non-viral band? But labs on rare occasions miss the p24. We showed that data very quickly.

And I think I must say, because I didn't want people to have the message that testing is all over the map, I think I said multiple times, the bottom line of Western blot testing is it is done very well, and it is done very well because this safety net is in place. It is when you get to making fine distinctions about individual bands that we clearly observe some problems.

DR. HOLLINGER: Dr. Busch?

DR. BUSCH: Yes, one comment in terms of the band patterns to seroconversion. I mean that is where you really get the meat of this, and we have looked at, you know, well over 50 seroconversion panels that have serial bleeds separated by several days as these various blots evolve, and there is some variability between the blots. In general, these blots are most sensitive to p24 in primary seroconversion, but in some cases you will see some envelope or pol come up fairly equivalently in time.

If you would look at recombinant assays which

have, you know, been submitted to FDA, they are often more sensitive to gp41, so that will be the first band that will be detected at the same point as p24. So the sensitivity of these assays varies by the antigen representation within the assay, not necessarily reflective of the antibody evolution in the people. But certainly in contemporary blots I think p24 is by far the most frequent to come up initially.

Now, the twist here is that these evolving seroconversions can happen in people who have non-specific non-viral bands. You saw the example that was shown by one of the companies where there was actually, throughout the seroconversion panel, there was a non-viral band all the way along the top. So you really have to look at these panels and interpret evolving new bands in the context of the EIA seroconversion to understand, you know, what new bands are relevant.

And I do think it is p24, in all the currently licensed blots, and that those bands are very clear. But of course during seroconversion you can have initially a very weak p24 band, because we are just catching bleeds right at that point where these antibodies are first detectable. But in the real world this is, you know, it is p24 and it is really very straightforward.

DR. HOLLINGER: I want to be sure I am clear here, Mike. You are saying, then, that the p24 is always there in

the early seroconversion. There may be other bands there--

DR. BUSCH: Right.

DR. HOLLINGER: --but at least the p24 is always there?

DR. BUSCH: At least in my experience, in these viral lysate Western blots, yes.

DR. HOLLINGER: And I think that is what Dr. Stramer said, also. Okay, thank you.

Yes? Yes, Dr. Fitzpatrick.

DR. FITZPATRICK: Just as a laboratorian and a blood banker, I think a couple of the key things are, in looking at the overall performance from the Public Health Service labs, we had eight positive samples that were called non-reactive. It is highly unlikely those were because of a non-viral band, but we don't have a root cause analysis. We don't know why they were called non-reactive. If we look at error and accident reports, my guess would be there was a sample ID mix-up.

We have talked about Dr. Chamberland's issues on the clinical side, and I think the fear here would be that if the Western blot is reported as negative and there is no note that there were non-viral bands present, the donor or the patient would not be subject to coming back for follow-up. And in many cases we would probably still want to bring that individual back for follow-up, if there were non-viral

bands present, because that EIA is still going to be repeat reactive.

And I think we are overemphasizing the fact that these are going to be donors that are now going to be reentered into the pool. Dr. Stramer told us that most of them continue to be repeat reactive EIA. So we have to construct a message to the donor that says, "Your ELISA is reactive, your Western blot has non-viral bands, which means you probably don't have disease, but if you continue to donate, your blood is still going to react, and you have a f false biological positive," just like we do with the RPR and the FTA ABS.

And so I think we might be sending the wrong message by giving the clinician and the blood bank director the result of a negative Western blot, unless they have the information that is before them, and I think it is the duty of the lab to report the true information and have the ability to do that, and then to interpret that. And if your lab isn't proficient, then we need to bring labs up to proficiency level. We shouldn't make our decision based on the fact that there are some bad labs out there.

DR. HOLLINGER: And I don't know whether that follows through, some of that, what you point out, follows through, but remember all of these got into the Western blot because the EIA is positive. And so somebody would,

theoretically should follow this, you would hope would follow this up anyway, because EIA positivity usually precedes the Western blot becoming positive, so it could be in the early stage of infection. So you would follow this up anyway with either repeat bleeding or NAT testing or something of that nature, you would hope. I mean, I would think.

Okay. Yes, go ahead, Marion, and then we will--

DR. KOERPER: One more point of clarification. When labs are reporting the indeterminate results right now, is that it? It is just the one word, "indeterminate"? So could we have an option of saying, rather than negative, that labs should report "Indeterminate (Viral Bands Present)" or "Indeterminate (Non-Viral Bands Present)"?

DR. HOLLINGER: That is one option.

DR. KOERPER: In other words, can we vote no to this and then have a new question? I don't know procedurally how we do this.

DR. HOLLINGER: Yes, of course. Of course.

DR. KOERPER: Okay.

DR. HOLLINGER: Yes, David?

DR. SCHMIDT: I was just going to say, as far as blood donors are concerned, you know, if the EIA is positive and the Western blot has a non-viral band determined as negative, they are eligible for reentry but they still have

to be tested again. So I think voting for this would not jeopardize the blood supply at all. I agree that if it is an issue, it is an issue with patient testing.

DR. HOLLINGER: Thank you. Yes, Toby, and then we are going to go and--

DR. SIMON: The comment has been made about giving the donor all the information from the test, but from what I have heard from the experts, non-viral bands is not information. It is something that is there that is meaningless, and I don't know what one would do with that information. I don't know what a clinician would do with it. It is useless information. It is non-information, basically, so I see no advantage to giving the clinician taking care of a patient or a blood bank physician that information. So it seems to me with either the donor situation or the patient situation, the answer to the question could be yes, we really don't need to give anyone the information about non-viral bands.

DR. HOLLINGER: It is like having a lot of other things we see as clinicians when we take care of patients. We sometimes ignore even discussing it with the patient because it is not meaningful. I mean, we know it is there and we know it is positive or has some abnormalities, but we are certainly not going to discuss it with a patient because it has no significance.

DR. SIMON: It is not necessarily reported that way. It is reported as an indeterminate blot, and that is what the clinician deals with.

DR. HOLLINGER: Yes. Mary?

DR. CHAMBERLAND: But reporting it as an indeterminate blot gives you the safety net of right now, the way the recommendations are written, of essentially counseling the individual that they need to come back to be retested, and the period, the interval for that second test is currently under revision.

To report out negative, I see that very much tied as negative. The counseling message is, "You don't have to come back. There's no need to be retested." Now, again, as Lou says, if you are dealing with a high risk individual who is continuing to engage in high risk behavior, counseling messages obviously need to be formulated certainly about decreasing high risk behavior, but also the possible need for follow-up testing.

But I think the concern that I have is, negative means no follow-up, so voting for this position really would eliminate what I view as a safety net, again not really applicable to the donor setting but to the individual clinical diagnostic setting.

DR. HOLLINGER: But I think I would go a little further. I think what is being asked is how you would call

the Western blot test. That doesn't mean that you are going to tell a patient who is EIA reactive positive, I mean repeatedly reactive, who has a Western blot that is, quote, you could call it negative, just the Western blot test.

That doesn't tell the patient he is free and has nothing else to worry about. I think that would be wrong, I agree with you entirely, to give that message to the individual because you find no viral or you find only non-viral bands on the Western blot. You still have to follow up what that EIA indicates with some test in the future, I would think.

DR. CHAMBERLAND: I guess I was just reacting to the way the FDA has constructed the series of questions. It looked like you proceeded to different counseling messages if you voted--if the majority vote was no, that FDA should not permit indeterminate blots to be interpreted as negative, then you proceeded on to retaining "indeterminate" but with different counseling messages.

So I think that is how they envisioned the flow of it, not that if it is read out as negative, you would then have a series of counseling messages: "Your test is negative but it showed only non-viral bands, hence, you should consider retesting," or whatever. Is that correct, Jay? I mean--

DR. EPSTEIN: I think we are looking for a clean

answer in the sense that a negative test would imply a negative counseling message. Now, having said that, obviously clinicians have to take into account all the available information, and if someone has high risk behavior, they should probably be rescreened later. But it is really not driven by the fact that they had a repeatedly reactive EIA, if they had a clean negative interpreted Western blot. Now, I am putting aside for a moment the issue of test sequence, because we know that there are some EIAs that are more sensitive than some blots, and you would have to consider that, too.

DR. HOLLINGER: Jay, do you really want to couch it in that fashion, that a negative test means a negative counseling? I mean, this could be a person who has viral bands and EIA positivity with non-viral bands anyway, and is in the very early stages of his infection, in which he may have virus circulating. I mean, you could have non-viral bands and still be infected, and it will show up that way.

So if you are saying--if that is how you are couching this question, to the point that if this is voted on as that negative means no counseling, then I would have to look at this a lot differently. I am looking at this as strictly a test question here in terms of the Western blot, that if there are non-viral bands present, it could be reported as negative. Now, what you do after that, it comes

with the next question.

DR. EPSTEIN: Right. I think that what you have said is correct. We need to keep this simple. We have not asked the committee to consider how we deal with counseling or medical decision-making concerning retesting. We are only asking whether the blot, as a stand-alone test, can be properly interpreted as negative based on a reader's ability to determine that it is non-viral bands only. I think we should limit our purview to that test and its interpretation.

The current problem that we have is that the category of "blot indeterminate" is wide-ranging, and includes true positives that are in seroconverters, it includes true positives that are in people with virus variance, it includes negatives where there are in fact viral bands due to cross-reactive antibodies, and it includes true negatives that have only non-viral bands. And all of that is confounded when the clinician gets a report of "indeterminate". They really don't know which it is.

And what we are asking is whether we can carve out the subset of non-viral bands and determine that at least in that instance the test can be called negative, based on good current science, and recognizing all the proficiency concerns that I think have been, you know, amply discussed. And I think that it will only confound matters if we try to

then go further and say, "Well, are we also telling doctors how to use all the available information?" We are not seeking to do that. We are just seeking to clarify the interpretation of the test.

DR. FITZPATRICK: Jay, I am a little fuzzy from lack of sleep, but if it is an ELISA repeat reactive with a negative Western blot, there is no donor notification required, correct?

DR. EPSTEIN: There is donor notification required--well, it will be required that you inform a deferred donor of the fact of the deferral. That was one of the proposed rules that we published August 19th of last year. It is of course a current recommendation of the FDA that the donor be notified of the fact of their deferral and be informed of the reason why. So you would still have to notify a donor, and we will be requiring that you also counsel a donor.

DR. FITZPATRICK: For a repeat reactive ELISA with a negative Western blot?

DR. EPSTEIN: Yes.

DR. FITZPATRICK: Okay

DR. EPSTEIN: Yes, because that is still a condition of donor deferral.

DR. FITZPATRICK: Okay.

DR. HOLLINGER: Mike?

DR. BUSCH: Yes. I buzzed over it, but in the material I presented and distributed, we quantified--the current most widely used donor screening assay is the Abbot combi test, which is very sensitive, and in fact you have a three-day window between the time, based on large numbers of seroconversion panels, that EIA seroconverts before you have any bands on Western blot. So there is a three-day blot negative phase, and then there is only a five-day blot indeterminate phase before meet current criteria positivity.

So it is always--what you are trying to do is refine the specificity of the blot interpretation. Eliminating non-viral bands will not--you know, will improve that, and I think that the issue of having to recall and potentially counsel donors who are EIA reactive or any population is a given. There is a very remote potential that a person who is EIA reactive, blot negative, could be a true seroconverter, and that always needs to be considered.

DR. HOLLINGER: Any other, from the committee, any other--yes, Dr. Ng?

DR. NG: I just once again want to say your recommendation will cross over to the diagnostic arena. And Dr. Simon, actually in my experience the identification of non-viral band reactivity on Western blot has often triggered and identified patients with undiagnosed lupus and other autoimmune disorders. So there actually is value in

finding out what the reactivity pattern is in an indeterminate Western blot.

DR. HOLLINGER: Okay. I think we will vote on this, the first question here, and the question as stated, I will read it for the record. It is: "Should FDA permit indeterminate Western blots with only non-viral bands to be interpreted as negative?" All those who agree with that statement or with that question, raise your hand.

[A show of hands.]

DR. HOLLINGER: All opposed?

[A show of hands.]

DR. HOLLINGER: And those abstaining?

[No response.]

DR. HOLLINGER: And our two non-voting members?

MS. KNOWLES: No.

DR. HOLLINGER: Toby?

DR. SIMON: I vote yes.

DR. HOLLINGER: All right. Could we have a reading of this confusing--

DR. SMALLWOOD: According to my count, there were seven "yes" votes and there were seven "no" votes. The industry rep agreed with the "yes" votes and the consumer rep agreed with the "no" votes. Is that correct? There were no abstentions.

DR. HOLLINGER: Okay. Well, we hope we have

clarified this for you, Jay.

[Laughter.]

DR. HOLLINGER: No, I think underlying this there is a lot of issues here, and perhaps this will come up with the next issue. Is there another? Or do we have to even deal with the next question, basically? If not, all right, so we can--oh, that is right, it was 7-7, wasn't it? Okay. I tried to push this one through, but--

DR. MIED: This refers to the middle ground approach that I referred to earlier, that the counseling message could be stratified based on the band pattern, that different counseling messages that reflect the likelihood of infection along with the recommendation to be retested could be provided to the donors.

DR. HOLLINGER: Yes.

DR. MITCHELL: So the question is, if not, should blot interpretation such as "Indeterminate (Viral Bands Present)" and "Indeterminate (Viral Bands Absent)" be reported with distinct counseling messages?

DR. HOLLINGER: Yes. Obviously, you know, since this was essentially a wash here in the voting, I think what I would like to do is, I think people have sort of expressed their own opinions here, but I think you have the feeling a little bit, Jay, of what the issues are. It has a lot to do with what is going to happen afterwards, and that people are

proficient, and if they are not, then that is a problem. Second, it said the FDA would permit people to report non-viral bands as negative. If the lab isn't confident, they can report that out as indeterminate or report it out as negative with non-viral bands. You know, a pathologist has that prerogative to do that. So I think that number one would work for patient testing labs and it would work well for the blood center, and it would give donors honest messages.

DR. HOLLINGER: Yes, Dr. Tuazon?

DR. TUAZON: I voted yes because, as I said earlier, in clinical practice we use the NAT to confirm a positive EIA.

DR. HOLLINGER: Dr. Fitzpatrick?

DR. FITZPATRICK: I voted yes because there is clear evidence that it is a negative result, and I think the labs should report it with that. And there are a number of other laboratory tests that we do that are subjective, and we don't report them out in a different manner because some labs are more proficient than others; we report them out as either negative or positive because that is what the results are. And so I think we owe it to report out the true result as much and in as proficient a manner as we can, and rely on proficiency surveys and those things to bring proficiency up to the level it should be.

DR. HOLLINGER: Yes, Marion?

DR. KOERPER: I voted no because I think that this is the true result. This is the viral bands are present or viral bands are absent. As a clinician, I agree with Dr. Ng completely. There are many times that an equivocal test result when you are asking one question leads you to ask the next question, which is the correct question, which is not does the patient have HIV but does the patient have lupus, for instance? And many times I have to get on the phone and call the supervisor and say, "Okay, you reported this as negative, but tell me, did you see," da-dah, da-dah. And so I think this is the true answer, is that there is non-viral bands present, and then it is up to the clinician to determine how that influences the next step in dealing with the patient. And just to say negative to me implies that it is a blank strip, and so I feel that this is the more accurate answer, and that is why I voted no.

DR. HOLLINGER: Thank you, Marion. Anyone else like to comment? Yes, Jeanne?

DR. LINDEN: Like David, I interpreted the question as permissive, that blood banks could do that if they wanted to. It would not require people to. And if there were demand in clinical labs that there is some clinical value to knowing about the viral bands, I mean we didn't hear and data or information about the significance

of the non-viral bands, but if there is some and there is demand for that, then the clinical labs could still report that. So I thought that this would, in the blood donor situation, allow these donors to be put in a different category, and I am particularly concerned about the eligibility for reentry, even if most of them aren't going to be able to do that anyway.

DR. HOLLINGER: Thank you, Jeanne.

Well, let's assume that they are able to distinguish the viral bands and non-viral bands, and you determine it, that therefore you can decide if there were viral bands present or there were viral bands absent, and then you then mark them "indeterminate". So we will go with this second question. I would like to see maybe how the committee would vote under those circumstances. And if that is the case, then should blot interpretations such as "Indeterminate (Viral Bands Present)" and "Indeterminate (Viral Bands Absent) be reported with distinct counseling messages? So with that in mind, all those who would vote yes for that, raise your hands.

[A show of hands.]

DR. HOLLINGER: All those no?

[No response.]

DR. HOLLINGER: Dr. Simon?

DR. SIMON: Yes.

DR. HOLLINGER: And Ms. Knowles?

MS. KNOWLES: Yes.

DR. HOLLINGER: Oh, and we have one abstained. Oh, I'm sorry, there were two abstained.

DR. SMALLWOOD: Please raise your hands.

DR. HOLLINGER: Yes. Thanks. And could you read those, please?

DR. SMALLWOOD: Results of voting for question number two, as read: Should blot interpretations such as "Indeterminate (Viral Bands Present)" and "Indeterminate (Viral Bands Absent) be reported with distinct counseling messages?"

There were 12 "yes" votes. There were no "no" votes. Two abstentions. The industry rep agreed with the "yes" vote and the consumer rep agreed with the "yes" vote.

DR. HOLLINGER: I want to thank the committee for this stimulating discussion this morning. We are going to take a break now until 2 o'clock. The cafeteria is open until 2:00, and there are some places around the area. Let's meet back here at 2 o'clock to start on the session about hepatitis.

[Whereupon, at 1:00 p.m., the committee adjourned, to reconvene at 2:00 p.m. the same day.]

# A F T E R N O O N  S E S S I O N

2:00 P.M.

DR. SMALLWOOD: Would the committee members in the room return to their seats, please? For this afternoon's session, we have two potentially involved topics, and so we would like to continue on so that we can take the best advantage of the time that we have allotted. We don't want you to get up and walk out, because we tried to make this a major production for you, so we want you to stay until the end.

At this time I will turn the proceedings over to the chairperson, Dr. Hollinger.

DR. HOLLINGER: Thank you, Dr. Smallwood.

The first topic this afternoon is on the history of hepatitis, the issue about whether or not the question of hepatitis should still be utilized, and to start us off, Robin Biswas will give us an introduction and background to the issues, please.

DR. BISWAS: Well, good afternoon. We will be spending this afternoon discussing viral hepatitis topics related to blood donation, and I think that the underlying theme here is, is how far the diagnosis and testing and the understanding of viral hepatitis has progressed in the last 30 years or so.

Now the first item on the agenda is donor

suitability and history of viral hepatitis. I will give you some background information and our current thinking on the topic, and I will present two questions to the committee. After that, Ian Williams of CDC and Harvey Alter of the NIH will present data, followed by discussions and your recommendations. I hope you don't vote 7 to 7.

Now these are the two regulations that preclude persons with a history of viral hepatitis from donating whole blood or source plasma. The one on the left, 21 CFR 640, I won't read it all out, (c)(1), is for donations of whole blood and blood components for transfusion, and the one on the right, the one with the 63 and the (c) and the (11) in it, for donations of plasma collected for further manufacture into injectable plasma derivatives. These collections are pooled and manufactured, processed further into things like albumin, immunoglobulin, and clotting factors.

Now it is at least since the early 1950s that blood establishments have used a history of hepatitis criterion or a history of hepatitis donor question for determining donor suitability, and it is at least since the late 1950s that a history of hepatitis donor exclusion regulation, that there has been a government regulation in place. And it is at least since the early 1960s that blood establishments included a history of jaundice, or sometimes

called yellow jaundice, in the questions in determining donor suitability. I should explain that jaundice is a non-specific physical symptom of viral hepatitis, and can be caused by very many reasons other than viral hepatitis.

But the important point here is that these regulations and blood establishment questions regarding donor history of past hepatitis or jaundice were put in place long before any tests were developed that detected any hepatitis viruses, and before much was known about the infections caused by these viruses. For example, one question was, did individuals who had clinical hepatitis, had clinical symptomatic hepatitis, remain chronically infected after apparent clinical recovery?

Now since that time, tests for several hepatitis viruses have been developed. There have been tests developed for hepatitis A, B, C, Delta virus, E, and I won't mention G because it is probably not a hepatitis virus. And, in particular, very sensitive tests for hepatitis B and hepatitis C have been developed and licensed and implemented in blood establishments. These two viruses, hepatitis B and C, are the two blood borne viruses which cause almost all hepatitis infections that can occur in recipients.

Now today all donors of blood and blood components for transfusion are tested for hepatitis B surface antigen, antibody to hepatitis B core antigen, antibody to hepatitis

C virus, and almost all whole blood is also tested for alanine aminotransferase, which is a non-specific marker for liver damage.

Plasma for further manufacture, which I have said is pooled and then processed into various plasma derivatives, is tested for hepatitis B surface antigen, anti-HCV, and ALT. It is not tested for anti-core because most anti-core positive units also contain the neutralizing anti-HBs antibodies which can neutralize HBV. Withholding such units from pools from which the plasma derivatives are manufactured would make the titer, would cause the titer of anti-HBs to be diminished and probably decrease safety of the plasma product as well.

Now testing technology continues to advance, and with the application of investigation nucleic acid detection tests, the NAT tests, for screening blood and plasma under INDs using a pooled plasma testing format, all source plasma and almost all blood for transfusion in the U.S. is now tested for HCV as it is for HIV by NAT. HCV NAT is expected to further lower the already extremely low HCV transmission risk by detecting viruses in the so-called window period, that is, after the infection has indeed occurred but before antigen or antibodies are detectable in the circulation.

In regards to the utility of HBV NAT donor testing, this will be discussed later today. Suffice it to

say that some source plasma is already being tested for HBV NAT.

Because of the increasingly sensitive tests for viral hepatitis B and C, the risk of post-transfusion hepatitis overall is being rapidly reduced to barely detectable numbers. This fact, together with advancing knowledge about viral hepatitis, has raised questions about the necessity for excluding donors with a history of clinical hepatitis.

Therefore, FDA sponsored a workshop last July to discuss the issue and to examine any relevant data. Actually, the Blood Products Advisory Committee has discussed this issue several times in the past, in 1982, 1991, and 1992 BPAC meetings, and the committee has over the years recommended that FDA modify the interpretation of these regulations.

So, consistent with past BPAC recommendations, the regulations are currently interpreted as follows: A donor with a history of clinical viral hepatitis after 11 years of age, actually after the 11th birthday, should be deferred. That means that anyone with a history of hepatitis until their 11th birthday could still donate, could go ahead and donate. This was considered appropriate because of CDC data presented at the 1991 BPAC meeting indicating that almost all viral hepatitis that occurs in children under the age of

11 was hepatitis A. I should explain that what we were doing, what we did was to permit exemptions to the regulations under another regulation, 641.20.

At present the term "viral hepatitis" might include jaundice or a clinical diagnosis of hepatitis. Now, this was in response to the 1992 committee's recommendation not to interpret test results alone as a history of hepatitis, in the absence of clinical history or absence of a medical diagnosis, and the tests that we are talking about here are anti-core tests and ALT tests. Note that in a donor with a history of jaundice after the age of 11, if it is not possible to rule out the viral hepatitis as cause of the jaundice, the donor should be deferred.

Now the goals--not the goals, the goal--of last July's workshop was to discuss the following: Is there sufficient information today to consider eliminating the exclusion of donors who have a history of viral hepatitis?

Now an enormous amount of information on the etiology, biology, serology, epidemiology, and the testing and medical diagnosis of viral hepatitis was presented at the workshop. The multiple causes of jaundice, infectious and non-infectious, were listed and reviewed and discussed. The following is a necessarily extremely brief summary of the main points of that meeting.

Studies in the 1970s by Dr. Tabor, and I think the

Red Cross, and in the 1980s conducted by Dr. Gary Techmeier, showed that markers for hepatitis A, B and C and ALT elevations were more often present in donors with a history of hepatitis or jaundice that in donors with no such history. There is no recent data. None of us could--you know, we plowed through the literature and nobody could come up with any modern data on this. It was also stated that the regulations were probably useful in the past for preventing post-transfusion hepatitis.

Dr. Celso Bianco said that 13,000 whole blood donors were deferred in 1998--this is for the whole country --in 1998 solely for a history of hepatitis or jaundice. With the inclusion of NAT testing of donors, the remaining residual risk for hepatitis B virus would be 9 units per 1 million units, and for HCV, 3 units per 1 million units.

Another thing is that the incidence of acute HBV and HCV infections is declining in the United States. There are a couple of typos on this. I did this at the last minute yesterday afternoon. Sorry about that. So for HBV, from the mid to late 1980s, there were 32 cases per 100,000 acute symptomatic cases of viral hepatitis, and this went down to 15 cases of hepatitis B per 100,000 per year. For HCV the comparative numbers are 19 cases per 100,000--there should be an extra zero there--to only 2 per 100,000 per year. Well, you know, if these numbers remain the same or

even get less, then eventually this will affect the prevalence amongst blood donors.

It was also stated, another conclusion of the meeting was that apart from HBV and HCV, known viral hepatitis agents do not cause significant recipient risk. However, CDC reported that 3 percent of reported acute viral hepatitis cases in the U.S. are hepatitis non-A through E. These are individuals who have or are thought to have clinical symptoms of hepatitis, but are not positive in any test from A through E. There were also the mysterious media accounts of hepatitis virus referred to as "SEN-V" and hopefully we will be hearing more later today.

It was also stated at the meeting that any increase in post-transfusion hepatitis resulting from elimination of the history of hepatitis donor questions would be difficult to detect if the change is slight.

Now, as a result of the workshop and discussions that took place, it becomes apparent that there are four options. The first one, entirely eliminating exclusion for history of hepatitis. Second one, keep the exclusion. The third one, modify the exclusion by excluding donors with a history of clinical hepatitis for only a limited period; for example, for one year after disappearance of symptoms. The fourth option is to modify the exclusion by accepting donors whose previous viral hepatitis, for example, hepatitis A,

could be documented not to pose a current risk for recipient hepatitis, i.e., require documentation to demonstrate what the etiologic agent was at the time the potential donor was diagnosed with viral hepatitis.

I will now go through these four options again and briefly discuss each one of them. One, eliminate exclusion for a history of viral hepatitis. Well, one would stop deferral of about 13,000 whole blood donors per year who are highly likely safe. The problem is the lack of information about CDC's reported 3 percent acute non-A through E hepatitis and the accounts of SEN-V. And I will be repeating this refrain several times in the next few minutes.

Now the utility of the question, the donor question about history of hepatitis, is likely to be very low, but is it absent? I should have put a question mark after that. In the absence of data on the utility of the question for elimination of hepatitis non-A through E, it appears to us premature to drop the question. It seems that such agents do exist, and the question is, do they correlate with the history of symptomatic hepatitis, and how many chronic hepatitis non-A through E cases had a history of hepatitis with symptoms?

The same questions one can ask for SEN-V. One would also like to know if SEN-V and non-A through E, if the

non-A through E entity or entities, whether they are serious diseases or not. In regard to SEN-V, if it turns out, for example, that SEN-V is an agent of non-A through E, and if validated donor tests became available, then testing for it could accompany elimination of the donor question, provided SEN-V accounts for most of hepatitis non-A through E cases. Hopefully we will have a few answers in the next few hours or next few days or next few weeks.

Keeping the exclusion for history of viral hepatitis, well, you would retain a safety layer. The problem is continued deferral of many safe donors. We agree that the regulation as is, is outmoded. It is not useful for known agents. There are sensitive tests for hepatitis B virus and hepatitis C virus. It is probably very inefficient for unknown agents. If only these facts were considered, FDA would be prepared to permit removal of the donor question regarding past hepatitis. However, again in the absence of data on the utility of the question for elimination of hepatitis non-A through E, and in light of the SEN-V reports, it appears premature to drop the question.

Option number three: Modify the exclusion by excluding donors with a history of viral hepatitis for a limited time period, for example, one year after disappearance of symptoms. Should be easy to do. Would

retain probably many if not all of those donors after one year's disappearance of symptoms, but again we run into the SEN-V, CDC 3 percent unknowns, if in this case they are chronic. Would not capture non-A through E hepatitis that became chronic and persisted for one year, for more than one year. If the assumption is that an infection is chronic, setting a one-year limit is arbitrary.

Now the fourth option: Modify the exclusion by accepting donors whose previous viral hepatitis, e.g. hepatitis A, could be documented not to pose a current risk for recipient hepatitis. Well, we feel it is a safe and scientifically sound way of reconsidering deferred donors. However, acquiring evaluable documentation might be difficult.

While acknowledging the difficulties in implementation, as I just said, it is a sound scientific way for reconsidering deferred donors. FDA is considering permitting this approach, and although it is difficult, some donors could be reentered, and this would be yet another step forward in permitting safe donors with a history of hepatitis to donate, by reconciling current interpretation of the regulations with well-established medical knowledge.

So I will stop there, and shall I go ahead and show the questions?

So, question one: Does the committee agree that

the Food and Drug Administration should permit exemptions from the regulatory requirements to allow blood establishments to accept donors who report a history of viral hepatitis after the age of 11 years, if there is documentation that the hepatitis was caused by an agent other than hepatitis B virus or C virus for which the donor is no longer infectious?

Question number two: Please comment on any studies that could be useful to further clarify the utility of donor deferrals based on a history of viral hepatitis.

Thank you very much.

DR. HOLLINGER: Thank you, Robin.

I think we will move to the next presentation, and this is going to be by Ian Williams from the CDC on--well, I guess he is just going to tell us what he wants to.

DR. WILLIAMS: Actually Dr. Biswas asked me to come up here and tell you what we know about non-A through E hepatitis, and the piece I am going to talk to you about specifically is non-A through E hepatitis as identified in the Sentinel Counties Study of Acute Viral Hepatitis. Sentinel Counties is a study that focuses on community-acquired viral hepatitis, so that is going to be the thrust of my presentation today. But since the topic at hand is also a history of viral hepatitis, we also asked people in our study about that, so I will have a brief presentation at

the end focusing on that as well.

Since the data for today comes exclusively from the Sentinel Counties, I thought it would be worth spending a slide or two to explain to you what the Sentinel Counties Study is so you understand the source of the data. The Centers for Disease Control and Prevention conducts nationwide surveillance for acute viral hepatitis. However, certain issues limit the accuracy of this national data.

These issues specifically are things such as physicians fail to report cases they see to their State or local health department, therefore, CDC never hears about them so we don't count them as a case and don't know anything about them. Physicians may see cases and they fail to do the appropriate test, the correct test to make a diagnosis, or they fail to apply uniform case definitions. This is especially true in cases of hepatitis C. And, finally, they don't collect uniform data, epidemiologic data, especially related to risk factors.

So to address these issues with national surveillance, CDC began a study called the Sentinel Counties Study in 1979. The primary aims of this study are listed on the slide: to determine the relative contribution of hepatitis A virus, hepatitis B virus, and hepatitis C virus, as well as other agents of non-A, non-B hepatitis in community acquired acute viral hepatitis. And the emphasis

here is community acquired. That is people in the general community. The second primary aim is to determine trends in the incidence and risk factors associated with both acute hepatitis A, B and C, as well as other agents of non-A, non-B hepatitis.

The study is currently conducted in six counties, and in these counties is where this intensive surveillance is done. Today I am going to present data primarily from four counties. These are Pinellas County, which is St. Petersburg; Jefferson County--Pinellas County, Florida, which is St. Petersburg, Florida; Jefferson County, which is Birmingham, Alabama; the city and county of Denver; and Pierce County, which is Takoma, Washington. Two other counties have been added to the study: Multnomah County, which is Portland, in 1996; and San Francisco in 1999. But the data today primarily comes from these four places in the United States.

Patients in this study, again, are people with acute symptomatic viral hepatitis reported in these six health departments through stimulated passive surveillance, so we go out and try to find every single case of acute viral hepatitis that we can. Patients in this study have to meet the following clinical criteria: They must have discrete onset of signs or symptoms of viral hepatitis; they must have an ALT or an AST more than 2.5 times upper limit

of normal; and we exclude other causes of liver injury through a physician interview, an interview of the patient, and other things.

All patients undergo extensive serologic testing, listed here on the slide, including anti-HIV, total, IgM; HBsAg, anti-HBc, both total and IgM; and anti-HCV. They also undergo an extensive epidemiologic interview which takes about an hour or so to complete.

And, germane to our discussion today, patients with non-A, non-B hepatitis also have additional follow-up every six months for six months for two years after their acute onset. Keep in mind these are all acute symptomatic patients. So they are followed two years afterwards. In each one of these follow-ups every six months they have an ALT and AST drawn, they are tested for other markers of viral hepatitis, including PCR on selected samples.

And also germane to our discussion today, there was a group of patients who were identified in 1985 and 1986 with acute non-A, non-B hepatitis, who have been followed every six months up to today. This is a group of about 130 people which we will also be talking about.

So let's get right to the data, now that I have hopefully described Sentinel Counties to you. This is the source of the data that Robin was talking about earlier. If you look at all of the data in the Sentinel Counties for the

period of 1982 to 1997, about 48 percent of all the viral hepatitis we see is hepatitis A; about 34 percent is hepatitis B; about 15 percent is hepatitis C; and about 3 percent is non-hepatitis A, B, C, D or E. You will notice hepatitis D and E are not on the slide because essentially we do not see them. They are not seen in the United States, or at least not seen in the Sentinel Counties.

What I am going to do today is focus exclusively on this 3 percent, to describe the clinical and demographic characteristics as well as risk factors associated with this group, and as a comparison, I am going to compare them with the 15 percent of people who have hepatitis C. So, again, there is going to be two groups, patients with acute non-A through E hepatitis identified in two cohorts: people identified in 1985 and 1986 followed to today, so with lots of longitudinal follow-up; as well as all patients in the Sentinel Counties from 1991 to 1997. For the hepatitis C group which I am going to compare and contrast them to, it is going to be all patients identified with acute hepatitis C, identified between 1991 and 1997.

Okay, so what can we say when comparing these two groups? Well, people with non-A through E hepatitis tend to be older that people with acute hepatitis C. About 38 percent with non-A through E hepatitis are more than 40 years of age, versus about 25 percent of people with acute

hepatitis C. Median age is about 38 years in those with non-A through E, versus about 33 years in those with hepatitis C, so people with non-A through E tend to be a little bit older.

They tend to be equally likely to be male or female. Roughly 54 percent of people with non-A through E hepatitis are male, versus about 53 percent with acute hepatitis C.

In terms of race, they tend to be more likely to be non-white, specifically African American in this situation. About 43 percent of people with acute non-A through E tend to be non-white, versus about 19 percent among people with acute hepatitis C, and this is highly statistically significant.

In terms of the clinical characteristics, people with acute non-A through E hepatitis tend to look a little milder. If you look at their peak ALT level in acute phase of illness, only about 52 percent have ALTs more than 16 times upper limit of normal, versus about 68 percent among those who have acute hepatitis C. And if you look at their peak ALTs, peak ALTs among A through E tend to be about 940 compared to about 1193 among those with acute hepatitis C.

They tend to be about equally likely to be jaundiced. About 80 percent of people with non-A through E have bilirubins of greater than or equal to 3.0, versus

about 70 percent or 71 percent of those with acute hepatitis C, and again the median bilirubin is about 6 among non-A through E versus 5.2 among those with hepatitis C, but these aren't different than each other.

In terms of patients hospitalized, the people with non-A through E are about equally likely to be hospitalized as those with acute hepatitis C. About 25 percent were hospitalized, versus about 18 percent of those with acute hepatitis C. However, people with acute non-A through E are much less likely to develop chronic infection. Only about 22 percent went on to develop chronic infection, and these were people with at least two follow-up visits after their acute onset of illness. This is contrasted with 49 percent of people with hepatitis C in our cohort who went on to develop chronic infection--chronic hepatitis, sorry.

Okay, what about risk factors? Well, I pulled up common risk factors for hepatitis C for comparison, and to make matters a little more confusing, since blood transfusion has changed as a risk factor quite dramatically over time, I went back in and threw in the hepatitis C patients or the best as we can determine hepatitis C patients from 1985 and 1986, back in this group, so we are comparing risk factors from essentially the same time periods in these two groups.

And what you will notice is, about 4 percent of

the acute non-A through E hepatitis had blood transfusion as their putative source, versus about 9 percent among those with acute hepatitis C. Again, if you look in just the group from 1991 to 1997, we have not seen a case of transfusion associated hepatitis C since 1992. But these groups are not different in terms of their risk factors for transfusion.

However, people with acute non-A through E hepatitis tend to be much more likely to be not injection drug users. Only about 6 percent of acute non-A through E's reported injection drug use as their source, versus 36 percent of those people who admitted to injecting drugs in six weeks to six months prior to onset of illness.

They were no more likely to be health care workers. And although they did have a higher prevalence of high risk sexual behavior, predominantly having two or more sexual partners in the last six weeks to six months prior to their onset of illness, versus 5 percent who had hepatitis C, these were not significantly different from each other.

So what sort of conclusions can you draw about people with acute non-A through E hepatitis, when compared to those patients with acute hepatitis C? Well, patients with acute non-A through E hepatitis tend to be older, more likely to be non-white, have lower peak ALT levels during acute illness, have lower frequency of chronic hepatitis,

and tend to be less likely to be injection drug users.

I should caution you about some limitations of the data. The first thing is, all patients in this study are acute and symptomatic, so they have to be acutely ill to be in our study. We don't know anything about asymptomatic patients.

Our case definition is extremely sensitive. You will recall, as I said earlier, anyone with greater than 2.5 times upper limit of normal of ALT or AST is included in this study. While this is a very sensitive case definition, it may result in some misclassification, specifically that some cases of chronic hepatitis C might rarely be falsely misclassified as acute. We try to guard against this as closely as possible by interviewing physicians, looking at previous records, but it might rarely happen. So there may be chronic patients mixed in with some of our acutes, rarely.

And, finally, cases classified as non-A through E hepatitis might rarely have an unreported non-viral cause of hepatitis. Again, we interview patients and physicians to look for non-viral causes, but some of them may not report non-viral causes. Or patients may have a viral cause for which they were not tested, such as EBV or CMV. They were not all tested for that. So there may be some misclassification in our non-A through E hepatitis.

Now, moving quickly at the end, I am going to talk briefly about what we know about history of hepatitis in the Sentinel Counties Study. And simple, we asked patients, "Have you ever been previously diagnosed with hepatitis?" So, again, we take patients, say, "Have you ever been previously diagnosed with hepatitis?"

And what I have done for this analysis is specifically focus on people with acute symptomatic hepatitis A, because people with hepatitis B and C tend to be a much different group than the general population. For example, roughly 60 percent of all acute hepatitis C cases are injection drug users, more or less, so they are not like the general population. So I focused my analysis for the next couple of slides just on people with acute hepatitis A, because they tend to be most like the general population at large. And keep in mind that all of these cases were tested for viral markers of both hepatitis B and C.

Okay, so what do they say when we ask people about, people with hepatitis A about, "Have you had a history of hepatitis?" Well, basically nobody reports a history of hepatitis, although it does increase a little bit as they get a little bit older. So roughly 5 to 10 percent of people, or less than 10 percent of people, 5 to 10 percent of people report any history of hepatitis. So people say, "Nope, haven't had it."