strikes and you're out. At the 56, if it's still NAT negative, EIA positive, RIBA negative or indeterminate--I mean Western Blot negative or indeterminate--they could be studied again at a later interval, and if there is some--if they've had a flu vaccine or something like that, theoretically it would eventually, could eventually disappear, if you thought that person was actually not infected.

Yes?

DR. HOLLINGER: On the time period, I know it's always difficult to put down a specific time period, but it was my impression that at least one or some of these HIV sero--I mean, the seroconversion might occur up to 60 days or so, which is a little over eight weeks. I just feel more comfortable making that at least three months in there. There's a confidence interval here. And if I'm wrong about that information, that everything is going to convert by 56 days, and if you're absolutely certain about that, then I'll feel comfortable with eight weeks.

[Laughter.]

Is that correct? I see you're nodding heads. It looks like a bunch of these people I

have in the back of my car, you know.

[Laughter.]

DR. STRAMER: I've never been in your car. Everyone will, every donor that I have ever seen--

DR. NELSON: Mike.

DR. STRAMER: From every donor that has been studied since we first identified plasma seroconversion series, you know, over 10 years ago, everything happens within 7 to 14 days. People become, especially on the screening tests we're using today, people become EIA repeat reactive very quickly, and then there may be a prolonged period of time of Western Blot indeterminate before they become fully Western Blot positive, but certainly the seroconversion to EIA repeat reactive on the screening tests we're using today is a very short process. Going to p24 antigen after NAT reactivity occurs within just several days, and then onwards to antibody testing again takes only a week or two weeks at the longest. The longest donor we've had has been 42 days, and it's only been 42 days because of the error in one week after the sample. It's just an inter-assay--it's a sampling frequency issue.

DR. NELSON: And in order to be considered

for reentry, somebody who was EIA reactive and indeterminate would have to go to negative in that 56 days, and really be infected, and NAT negative, according to this. So I think it's--I mean, it's probably--but we can vote on this, and then if you want to propose a different time period, we can vote on that, as well. Let's vote on 56 days.

Oh, do you have a question?

DR. MITCHELL: So if we vote on this, can somebody come in after eight weeks and get the follow-up test at the same time that they're donating a unit, and then just have two different tests?

DR. NELSON: No, no, no. What we're voting on now is that there has to be this interval, and the question doesn't say that it's part of a repeat donation.

DR. MITCHELL: But my question was, can it be? Can you, at the same day, on the same day, donate for the second and for a unit?

DR. NELSON: I don't think so.

DR. MIED: With this proposal, you wouldn't have the test result from the sample.

DR. NELSON: Right. You would need to get the result back, and it could be the next day. And

it has to be an EIA, so--

DR. KOERPER: The way this is written, the follow-up is a sample. It's not--

DR. NELSON: Yes, it's not a donation.

DR. KOERPER: But right now we're being asked to vote only on the time interval, not what it is that gets tested after the time interval.

DR. NELSON: Right, right.

DR. KOERPER: So if we want to propose to change the algorithm, that has to be a separate question. We're just being asked to vote on the time interval.

DR. MITCHELL: Yes, I understand. I understand that, but the question is, what is a sample? And I think that you answered it, that they need the results from that sample before they can collect a unit, and I think that that needs to be clear.

DR. NELSON: Okay. Let's vote. So the issue is, a minimum of 56 days. It could be a maximum of, I don't know, 10 years. All those voting yes?

[A show of hands.]

DR. NELSON: Voting no?

Abstentions?

Consumer representative?

MS. KNOWLES: Yes.

DR. NELSON: Industry?

DR. SIMON: Yes.

DR. SMALLWOOD: Result of voting on Question No. 3 pertaining to HIV test result, and the minimum time would be 56 days. It was a unanimous "yes" vote of 15 votes, no "noes", no abstentions, and both the consumer and industry representative agreed with the "yes" vote.

DR. NELSON: Okay, let's move to hepatitis C. Six months is the proposed interval. Comments?

Those voting yes on six months for hepatitis C?

[A show of hands.]

DR. NELSON: Those voting no?

Abstentions?

Consumer?

MS. KNOWLES: Yes.

DR. NELSON: Industry?

DR. SIMON: Yes.

DR. NELSON: Okay.

DR. SMALLWOOD: Results of voting on Question No. 7 pertaining to HIV test results, minimum time of six months, unanimous "yes" vote of

15 votes. Both the consumer and industry representative agreed with the "yes" vote.

DR. NELSON: Okay. For the final two questions, I'd like to lump them because I think they're pretty much identical, unless somebody has an objection to this. But the question is, should the blood establishment have the option of continuing to follow up a donor who is NAT negative, persistent either HIV repeat reactive, and not--with negative or indeterminate confirmatory assays, for potential reentry?

DR. HOLLINGER: Why is this being asked?

DR. NELSON: I don't know. I know the answer. I don't understand the question.

[Laughter.]

DR. NELSON: Jay?

DR. EPSTEIN: Currently we don't allow that.

DR. NELSON: Currently the FDA doesn't.

DR. HOLLINGER: I see.

DR. STRONCEK: Let me get a clarification. What you said is different than what's written here. Is that the intent of the FDA, to make that an anti-HIV, EIA repeatedly reactive, and Western Blot indeterminate or negative?

DR. NELSON: I think so. I think that--I did embellish it a little bit, but I think what the--if the issue is that this may be a false positive EIA, then it's an EIA positive test that is not--that has a negative confirmatory assay or is not--and I would be, I think that's an issue, because I think this could pick up, if the EIA is repeatedly positive, it could pick up a variant virus that maybe the primers in the NAT, you know, are not. Or it could pick up an HIV-2 or something like this. And so I would think that if--you know, I would be uncomfortable with a confirmed repeat reactive ELISA in, you know, a couple of occasions being--that person being eligible for reentry.

Mike?

DR. BUSCH: Yes, I think once they're confirmed, if on a retest you're EIA reactive and confirmed positive, you're permanently deferred. I think that's a given.

DR. NELSON: Right.

DR. BUSCH: I mean, if they have a persistent nonspecific EIA reactivity, with either a negative or a persistent indeterminate band, I mean, to me those donors are not infected, and a negative NAT.

DR. NELSON: Right.

DR. BUSCH: And the issue then becomes, you know, if you have a double hit on a false reactive EIA, are you permanently ineligible for reinstatement? And that's the problem I was alluding to earlier. The reality is that if you're not changing screening tests, you know, a good percentage of these people will persist false reactive, so in essence you're going to kill the donor. By trying to reinstate them, you're going to permanently defer them. And you're better off to wait years, until you change screening tests, and you're not offering the donor even the option. You know, as a program, I would not encourage trying to reinstate those donors because of the high probability they will defer and then be permanently--

DR. NELSON: Okay. Well, let's--a quick one, Celso?

DR. BIANCO: Just to add that many of the donors that were deferred in the early days of HIV because of antibodies to HLA and all that, they were--they cannot be reentered.

DR. NELSON: Right. Okay, let's vote on this one, and now we're talking about both HIV and

hepatitis C, if the committee agrees that this is a good strategy.

DR. SIMON: I think it's going to be impractical for most organizations to do this, but I think the reason for leaving it open here--

DR. NELSON: It's permissive, yes.

DR. SIMON: It's permissive, and for changes in technology that would allow you to clarify.

DR. NELSON: Right.

DR. SIMON: And again, this would probably be used for that particular special donor that serves a certain purpose, so in that respect I think it would be a positive move.

DR. NELSON: Okay. All of those voting yes on this question?

[A show of hands.]

DR. NELSON: Voting no?

Abstentions?

[A show of hands.]

DR. NELSON: Consumer rep?

MS. KNOWLES: Yes.

DR. SIMON: Yes.

DR. NELSON: Okay.

DR. SMALLWOOD: The understanding is that

the committee is voting on both Questions 4 and 8. Results of voting, 14 "yes" votes, no "noes", one abstention. Both the consumer and industry representative agreed with the "yes" vote.

DR. NELSON: Okay. Theoretically we're supposed to start the afternoon right now, but what I think we'll do is maybe have a 45 minute, 2:15. It means that we're probably not going to finish at 5:00, and somebody who told me they had a 5:30 plane, either is not going to testify or participate or should change their flight. So we'll be back here at 2:15. Thank you.

[Whereupon, at 1:35, the committee recessed, to reconvene at 2:15 p.m. the same day.]

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

[2:30 P.M.]

DR. NELSON: Okay, the first topic, and a substantial topic, this afternoon is a discussion of rapid HIV tests. The title is CLIA Criteria for In Vitro Diagnostic Tests: Applicability of Waivers to HIV Rapid Tests. And to introduce this topic and give background, Dr. Elliot Cowan from FDA.

CLINICAL LABORATORY IMPROVEMENT ACT CRITERIA FOR IN-VITRO DIAGNOSTIC TESTS: APPLICABILITY OF WAIVERS TO HIV RAPID TESTS

DR. COWAN: If you think it's hard to say "applicability," wait until you deal with waivers.

If we could go to the next slide, I'm just going to cut to the chase here. My purpose now is just to spend literally about two or three minutes to set the stage for you all, and then let the speakers take over.

Why are we here in the first place? First of all, I think you're all aware that there is a public health need for rapid HIV tests. We discussed this with you in prior meetings.

Some examples of this are for health care workers with needle stick injuries, and for

neonates delivered from at-risk women of unknown HIV status. It's critical to administer antiretroviral therapy to these people, for that therapy to be effective. This has to be done in a short period of time, whereas the common turnaround time for conventional HIV testing can be as much as a week.

Also, we have a situation where testing of individuals who are not likely to return for conventional test results--these are data that have been presented by the CDC, and I believe may be touched on in today's presentation.

Having said that, that there is a need for rapid HIV testing, it's unclear exactly what the best mechanism is to maximize the availability of that testing. So, given that, this is the way that today's session is going to be organized.

First, Dr. Tom Hearn from CDC is going to present a historical overview of CLIA waivers. Following that, there will be an overview of an FDA draft CLIA waiver guidance by Dr. Joe Hackett from FDA. Then Dr. Ida Onorato from the CDC will discuss public health strategic goals for HIV testing, followed by Judith Yost from the Health Care Financing Administration, who will go into

HCFA experience with CLIA waived tests in the laboratory, and also a discussion of moderate complexity tests and limited public health use of moderate complexity tests.

After that, I will conclude by offering some FDA perspectives on this issue, and then there will be a discussion, there will be the open public forum, and then presentation of the questions to you all.

So let me just go through the questions very briefly, and then we'll continue on with the rest of the speakers. The first question is, considering the known benefits and risks of rapid HIV testing, should FDA consider the possibility of removing all CLIA quality assurance oversight for such tests, that is, waive simple and accurate HIV testing from CLIA under its proposed criteria?

If I could just underline for you right now the "its proposed criteria" portion, and have you pay particular attention to the criteria that are going to be included under the FDA draft CLIA waiver, we're asking here whether a rapid HIV test should be included in this draft CLIA waiver guidance or if they should be pulled out, with certain exceptions.

The second question is, if not, if they should not be included under the FDA draft guidance, what are the criteria that should be applied in making waiver decisions for these tests? And specifically I'd like you to think about the sorts of data that you would like to see generated to support waiver.

And, finally, if rapid tests are not waived, is it appropriate to pursue other approaches under CLIA, for example, limited public health use, to promote wider access to rapid HIV testing? And there will be more of a discussion of what the limited public health use route is.

With that, I have completed my introduction.

DR. NELSON: Okay. Thank you, Dr. Cowan.

So the next speaker will be Dr. Thomas Hearn from CDC, who will present a historical overview of CLIA waivers.

DR. HEARN: I don't know if I'm so flattered to be part of history or not, but I have lived through CLIA up to now, and I do plan to live through it a little bit longer.

If I could have the slides, please, what I will try to do in this short presentation, and I

will try to keep the remarks brief, is talk a little bit about CLIA, the Clinical Laboratory Improvement Amendments of 1988, briefly focusing on those areas applicable to test categorization and waiver; also tell you a little bit about the process we used at CDC, when CDC had responsibility for making waiver determinations; and give you a sense of where things are now.

CLIA is actually the responsibility of three different agencies, the Health Care Financing Administration, the Centers for Disease Control, and the Food and Drug Administration. Early on, in the first rule that was published in 1992, there was a role for FDA because of limited resources. That role was taken on by CDC, but recently FDA has come back in, particularly in the area of the test categorization and waiver process.

The key features of the CLIA law--and this is law, these are the things that are in the law--that the law applied virtually to all clinical laboratories. Previously, laboratories were regulated by the fact that they were in interstate commerce or they were hospital laboratories. This expanded coverage to all sites that were doing laboratory testing.

The standards in the law specify that they would be based on complexity of testing, that is, more stringent standards for those tests which are really hard, less stringent standards for those which are more simple. There are special provisions for cytology. Sanctions are included in the law. And this is a user fee law, so this regulation is supported by user fees from the laboratories.

Going back to the CLIA statute and test complexity, the statute actually requires, again, that lab regulations be based on how difficult the test is to do, and specifically there is no provision for looking at a test because of the context in which it is used, that is, screening versus definitive diagnosis versus monitoring, or at the site at which it is used. So this has been a challenge, I think, under the CLIA law.

There was a provision, is a provision in the CLIA law that says that some tests may be so simple, so risk-free, that they could be considered exempt from CLIA standards, and they are called waiver.

There are some guiding principles that were used in the development of the regulations

that implement the law. First, of course, is to assure quality testing, because that's what the law was about, but I think it would have made no sense to anyone to have not thought about ensuring access, making sure the standards were at a minimum achievable level but at a level that would assure quality, and that the regulations would be written in a way to accommodate new technology and not hamper and impede it.

A lot of work went into the development of a complexity model, trying to decide how tests would fall under regulation, and I'm going to start at the bottom. The group of tests which are highly complex, require sophisticated equipment, judgment in doing tests, etcetera, the standards are written under the regulation so that they encompass QC, QA, proficiency testing, and personnel standards.

A less stringent criteria is for moderate complexity tests, and I'll tell you how that distinction is made in a little bit, but the big difference in moderate and high complexity are in the personnel standards, with some slight differences in quality control requirements. Labs doing only moderately complex tests were given some period of time to be able to achieve all of the

quality control standards.

Again, here is this "waived" category, and the only thing required under CLIA is that the laboratories or sites that are doing only waived testing, register and follow good laboratory practice.

I could have mentioned on the previous slide, and we do not need to go back to it, even with those provisions, there was a concern of, gee, are all the sites that need to be doing testing and can do quality testing under moderate complexity, are they able to do all the administrative sorts of things in order to comply with CLIA.

So a limited public health certificate was developed so that labs could coalesce together, as long as they did very few different types of procedures, 15 or less, and they could be covered by an umbrella certificate by a lab that does high complexity testing. More to come on that in another presentation, I believe.

Waiver requirements, again, the only thing that waived labs must do, and again, waived sites, is they must register, and I think there's a $50 every two year fee. They are not inspected, and they are exempt from all of the CLIA standards, and

that is in the areas of personnel, proficiency testing, quality control.

To kind of set the stage properly, I think there has been some confusion about test categorization and waiver. These aren't sequential processes. First of all, all tests are categorized, and at the time essentially of a 510K, PMA, every test is assigned to a complexity category of either high or moderate. We had much experience doing that because we had to do all the backlog of tests that existed at the time the '92 rule was written.

Additionally, sponsors or manufacturers may request that their products be considered for waiver, and the general criteria for waiver are defined in the law. There is statutory language. There is, further, a proposed rule for guidance, and then tests are reviewed and determinations are made. We'll see how this plays out in just a few more slides.

Just to let you know, because test categorization has really been the bulk of the work, almost 27,000 tests were categorized, essentially every product, every test was looked at with these seven criteria. There was a Leichert

scale established for each of the seven, of one to three. And I'm not going to show you a lot of data but there's a pretty nice split, so that those products which fell below a score of 13 I think ended up in the moderate category, and those above, in high complexity. And quite frankly, there was very little noise or feedback or, even more bluntly, complaints about the categorization of procedures as high or moderate.

The law for waivers states that tests are waived if they are, first of all, approved by the FDA for home use. So any product that is cleared for home use is waived. Second, simple waived tests are those simple tests that have an insignificant risk of an erroneous result, and that's the overarching statement, including those that employ simple, accurate methodologies with negligible likelihood of erroneous results by the user, or those which HHS has determined pose no unreasonable risk of harm to patients that perform correctly.

The last bullet, I'll tell you quite frankly, no one could ever agree that a test didn't have some potential for harm if performed incorrectly. Consequently, much emphasis was

placed on the requirement of accuracy. If a test was simple, foolproof, accurate, then that seemed to diminish the concern about risk of harm.

This is just one more meeting in the history of a lot of different steps about waiver. CDC, after consultation with the CLIA Advisory Committee, after looking over the initial 60,000 comments to a proposed CLIA rule, the 16,000 comments to the 1992 rule, developed guidance, a proposed rule for making waiver determinations, and published it, and I believe that we got 44 comments to that, so we felt like were getting closer to something that worked for most people. I actually did read a lot of those 60,000 letters, by the way.

And then there is a further legislative history, particularly with FDAMA, and now we've been in this process of trying to refine what the right guidance is for making waiver determinations.

With regard to simplicity, this is really a fairly commonsense approach, I think, that for a product to qualify or be considered for waiver, there was a requirement in the 1995 rule, proposed rule, that specimens not require any special handling, processing. In other words, they were either whole blood, urine, not serum samples, no

filtration. That the analyst not have to do anything in the process of doing the test, to adjust a piece of equipment, to do something which would require independent judgment. That there be fail-safe mechanisms, so that if the test didn't work, essentially a result wouldn't be issued. And that the instructions and the numbers of steps be very simple and straightforward.

There are requirements also in the proposed rule for accuracy and precision, and again, these requirements we viewed as a way to lower the risk. In the CDC proposal, we looked at field studies where data were collected at three sites, using at least 20 participants who were lay users or the kinds of people who would be doing waived testing.

For accuracy, we did require the sponsor to show data that would illustrate how the results that you would obtain with their product compared to a reference material, a reference method, the closest they could get to accuracy, and then these data were evaluated statistically.

Again, to summarize, CDC had the responsibility for categorizing and making waiver determinations essentially from the proposed--from

the publication of the 1992 CLIA regulations until January 2000, and even after January 2000 we worked closely together with FDA for a period of time in transition. At CDC, we classified or categorized almost 26,000 tests, looked at that many individual procedures.

And I think there's a misconception. We didn't waive any tests. There were 733 test systems that got approved for waiver. Now, 612 of these were tests which were like those published in this 1992 rule, and I'll show you that list in a minute. There were 109 test systems that we used this guidance that we published in 1995 to make the determination. And then there were 12 that got waived because they were cleared and approved by FDA for home use.

This is simply the list of tests that were published in the 1992 CLIA rule. These were published, this list and others were included in an earlier proposed rule, and these are the ones the department determined met their sense of what "waived" could be at that time, and quite frankly I think there was also a sense of grandfathering tests which were a standard of practice, were in use, and not waiving them would have disrupted

practice.

Here is a list of those tests, waived tests, which were approved for home use, and you can see this is a fairly diverse list of tests: prothrombin time, ketone, cholesterol, another diabetes test, cholesterol, catalase, and a bladder tumor antigen test.

This is the list of analytes, kinds of things that are measured, that came through the proposed rule process. It is a list of about 19 different things, although this and this are actually vaginal pH sorts of measurements, not too different. But as you could see, quite frankly this list contains a lot of things that, pre-CLIA, I might not have envisioned would be on here. But the important part is that they met the legal criteria and also met the published guidance criteria.

So where are we now? We started out, and there was less than 1 percent waived tests. Now there are about 3 percent waived tests. The bulk of tests are moderate complexity tests, with about a fourth of them being high complexity.

I believe Dr. Hackett is going to talk a good bit about where they are in their draft

guidance document. The main thing here is just a reiteration that for waiver, we look at simplicity, risk, and in our case, in CDC's case, we looked at that in terms of accuracy and precision. We looked at accuracy by looking at reference material and method comparisons. We looked at how the fail-safe mechanisms were handled. And if there wasn't a built-in shutoff, fail-safe mechanism, we approved tests where the manufacturer required that QC be done.

And flex studies were also supplied by manufacturers to show how much variation and tolerance could you have in environmental conditions, amount of sample applied, those sorts of things, so we would get a sense of just how robust the test was.

Last slide, clearly there are a lot of challenges in this area. Maintaining consistency in decisions. This was a brand new process for us. Starting and doing 26,000 categorized tests, and then the waiver process, was tough. I think we did a fairly good job. We had a fairly tight quality control of the decision-making process, both for waiver and test categorization. Independently, analysts looked at all the data that were

submitted. If there was agreement, they went on to another level of review within the division, and then another review at CDC.

So I felt like maintaining consistency of decisions went well. That there is always the challenge of new tests and technology you wouldn't have imagined. There is certainly an increasing complexity to the waiver reviews. And I think that we do need to have more discussion about public health benefits and concerns.

Thank you very much. I will be glad to answer questions.

DR. NELSON: Thank you, Dr. Hearn.

Questions from the committee? Yes, Mary?

DR. CHAMBERLAND: Tom, can you maybe augment or amplify a little bit, under the 1995 proposed rule, how accuracy was defined, if you will? You said it had--in your slide, it made the point that tests were--the test that was being considered for waiver were compared with reference material. Is this really--were you trying to establish things like sensitivity, specificity, predictive value? Is that how accuracy was--

DR. HEARN: We were looking at that. We were looking at how close to target value results

were, when compared with results obtained with reference materials or reference methods. And we were interested in sensitivity and specificity.

Quite frankly, the reviews got harder and harder. We started with things like cholesterol, and as you get towards infectious disease testing, it was hard to ignore thinking about predictive value, particularly for diseases and tests which in one setting the test would look really good, but once a test is waived and you think about it being used in a setting where the prevalence is very low, how good is that test, really?

So we didn't set a bar, Mary. If you're saying, did we say--

DR. CHAMBERLAND: No, but to--for example, in the situation that we are going to be, the committee is going to be asked to review, the rapid assays and their potential applicability for waiver, under the 1995 proposed rule, would rapid assays have been evaluated, or a standard panel, a well characterized panel, let's say, of blood samples would be available and tested by both rapid assay as well as for HIV, EIA, Western Blot, whatever, and then look at those, compare those with respect to the rapid assay sensitivity,

specificity? Is that--

DR. HEARN: Clearly, we did look data like that, because data are important, and if you see a Strep test up there, Strep came in, were clearly reviewed, see how they performed with panels of samples, but we didn't have a magic formula. We had not worked out, well, how many panels should you look at, how many samples should you look at.

DR. CHAMBERLAND: Right.

DR. HEARN: And quite frankly, because we had a proposed rule, we were looking for public input to exactly those kinds of things. In fact, in our proposed rule relative to this meeting, we did ask for what are the parameters, give us some feedback. Also we asked about, let us know about public health concerns, or even health care concerns or benefits that would be an outcome of using the process that we described.

So we weren't pretending that we had all the magic answers, and so we would welcome input here, and I'm sure FDA will, too.

DR. NELSON: Thank you very much, Dr. Hearn.

The next speaker will be Dr. Joseph Hackett, overview of FDA draft guidance for CLIA,

criteria for waiver.

DR. HACKETT: Good afternoon. With the passage of the Food and Drug Modernization Act, there were some slight changes in the language of the CLIA '88 legislation, and the result that we decided to look into the matter and found that for accuracy, we were going to be comparing how the test performed in the hands of a user versus how it performed in the hands of a professional. And I will elaborate on that or explain a little bit more as we go along.

So we call these alternative criteria that manufacturers could use, but at the present time we are following ourselves the criteria set up by HCFA and as used by CDC before us, so that's what we're using now. We're following CDC criteria until our own criteria, our own guidance, are up and formalized.

In the next slide I can give you kind of a status of where we are. We had a draft guidance that was published early this year on the internet and then announced formally in the Federal Register in January, with a comment period which came to an end last week, and we had several dozen comments, which means we must be getting closer, too. And we

hope to finalize this in the fall of this year, and have final guidance, so we would have two criteria available for looking for waiver by a manufacturer, either the CDC criteria or the FDA criteria.

Now, the components, some of these may sound very similar to what Dr. Hearn told you, because we really aren't that different from what CDC criteria had already proposed. We just differ slightly in some areas. Simplicity, the test has to be simple. There must be an insignificant risk of erroneous result. Accuracy. Again, we and CDC define that differently. CDC is looking at a reference material, and we are looking at comparison between the untrained user and the professional, and see how close they agree. And then finally, for labeling, we have some more information there to try to make the test easier to use.

The first component, simplicity, must be fully automated or self-contained, must be very simple to use. We keep stressing simplicity. Uses direct, unprocessed specimens. That's either whole blood or urine. We don't use serum because serum is a process step where you have to let the blood clot and take off the serum. So it must be very,

very simple.

Next, there must be no operator intervention during the analysis, so it has to be an almost hands-off type of activity, hands-off type of test. We keep again stressing simplicity.

No maintenance should be required. If the test breaks down or the instrument breaks down, you would notify the manufacturer and they would come in and take care of it, but the user is not expected to do any kind of maintenance.

There must be a direct read-out of the result. You don't have to multiply or divide or draw graphs or figure things out that way. Just a direct, easy readout, easy to understand, again stressing simplicity.

Insignificant risk of erroneous results. We look at two major things. The hazard analysis, the wrong order of application. What happens if you put your reagents in in the wrong order? Will that mess up the test? If it does, will you get an answer? Should you get an answer?

Incorrect timing. If the test is supposed to be read at five minutes, can you read it at seven? Can you read it at two minutes? If you do, how much leeway do you have? How much robust

activity is built into the test itself?

The environmental factors, again Dr. Hearn mentioned. Heat, humidity, temperature, storage temperature, all these are important also.

Validate QC procedures. QC is very important to us, as it is to CDC. Will your QC indicate if there is a failure? Is there any alert, that you can detect that your product is not working? Internal controls, how well do they work?

Accuracy. For quantitative precision, as does CDC, we looked at three levels, a high positive, low positive, and an average somewhere around the cutoff. We're looking at untrained users versus professional. We have like 20 specimens, 20 people testing at a site, three samples, that adds up to 180, and this is again compared to the result the professional obtains.

For quantitative accuracy, again, untrained versus professional, we're looking at 300 individual readings by 300 individual people who are untrained, versus the results of the professional. And usually a manufacturer will have like three professionals, and the professionals will sit down and do 100 at one time.

For qualitative tests, we're looking

mainly starting out with a feasibility study, and we're defining positives and negatives. We have a strong positive, which is about 2 to 5 percent false negative reaction. We have a strong--a weakly positive, which is about 15-20 percent false positive results; the weakly negative, which is about 15 percent to 20 percent false positive results; and a strong negative, which still has 5 to 10 percent false positive results. So this is a good way we feel we really test the system.

Component four is the labeling. First of all, we want the users to read the directions. Don't jump into it. Decide what you're going to do. Be familiar with the test. There is a step-by-step procedure which is supposed to be written to the level of seventh grade understanding. QC procedures, very important to follow. Actions to be taken. What if the test doesn't work? What if something fails? What do you do? What happens?

We have two checklists. This one will list all the items that I have been discussing. Are these included in the application the manufacturer sends in? And the second, the labeling items, are these all taken care of? And we try to use these to make it very simple and easy

to find. You don't have to guess. For instance, I have a coin here. There is no guessing. You don't have to flip a coin, try to figure out what happened. No guesswork at all. Everything straight, easy to understand, nice and simple.

Any questions? Yell and scream?

DR. NELSON: Yes, Pat?

DR. CHARACHE: I'm not sure I fully understand that slide that showed the permissible false positive and false negative rates, the one earlier. Could you explain that again?

DR. HACKETT: Okay. We don't want to have a high level of all positives and a low level of all negatives. We want to try to divide up the screen, the area to be covered. So some of your, what you would call high positives or strong positives, also have some false negatives in there, too, just to see how both would affect. So you would have high positive, low positive, high negative, and low negative.

DR. CHARACHE: So that will be in your panel of samples that are going to be compared between an untrained user and a trained user? Okay, thank you.

DR. NELSON: I don't understand, with

accuracy, you know, what I would think of--and maybe this was the CDC's criteria--that you have some independent test, a gold standard, if you will, and you compare this to a gold standard. Now, you may be comparing a copper standard with a professional and copper standard with a lay person, but it's still a copper standard. Am I misunderstanding that?

DR. HACKETT: No, that's correct. You're comparing the results obtained by the lay user versus a professional.

DR. NELSON: But if the test is a lousy test, then you can still waive it, if they both got the same lousy results?

DR. HACKETT: If they both got the same results.

DR. CHARACHE: Actually, I am a member of CLIAC as well, and that's the Clinical Laboratory Advisory Committee that advises FDA and CDC and HCFA on the policies that pertain to CLIA. This was, I think, one of two key points that was raised by CLIAC and is in their report.

They recommended that the guidance document be changed so that the word "accuracy" be used as it is in Webster's dictionary, because as

it is defined now, it is really comparability between two people, one of three trained technologists who are doing the test and someone who is not a trained technologist. And it was felt that one should first determine if the test is accurate or not, and then see whether you get comparability as to different steps.

DR. NELSON: Yes, the word should be "reproducibility" maybe, rather than accuracy.

DR. CHARACHE: Or precision, or whatever.

DR. NELSON: Yes.

DR. MACIK: A couple of points. I guess one problem I have is the use of untrained and professional. What you're really looking at, it's not fair to say an untrained because it's a lay person or a nonprofessional who has received training. I mean, obviously they have to be shown how to use the instrument, what to do with it. So that is--you know, I would kind of look at phrasing that as the nonprofessional or lay versus the professional.

The other is, if you look at the accuracy of the test, there's two parts. We're talking somewhat about waiving a test, but then you also have the 510K for that instrument test reagent, in

which accuracy is addressed because then it has to be compared to some gold standard. And so are we really looking at when you go, when you define where waiver comes in, is it after the 510K or is it part of the 510K?

DR. HACKETT: This is after the 510K.

DR. MACIK: Okay, so the 510K would have already taken care of whether that instrument is an accurate instrument.

DR. HACKETT: Right.

DR. NELSON: Pat?

DR. CHARACHE: A second issue that perhaps we could help clarify is the definition of the risk of an erroneous result. CLIAC divides a test into three parts in the original '88 law: the pre-analytical, the analytical, and the post-analytical. And the post-analytical includes what happens if you give the wrong result to an individual. It's the social and medical implications of the patient getting the fact that he's HIV positive if he's not, or vice versa, that he's not positive if he is.

And, as I have heard the definition of risk, it addresses the analytical phase only, you know, how easy or difficult it is to get a wrong

result. Does the guidance document address the impact on the patient who receives the erroneous result, whether positive or negative, or the social implications of that?

DR. HACKETT: It's very limited, as far as extending to impact on the patient.

DR. NELSON: Mary?

DR. CHAMBERLAND: Yes. To follow up on these comments, because I agree with the comments that were made about the need to determine the test accuracy as we would traditionally define it and then to determine its precision and reproducibility, those are two different things, my question is, however, is the accuracy--is not FDA presented with data regarding a test's accuracy, meaning sensitivity, specificity, the usual things we consider, when the sponsor approaches FDA for licensure of the test? So wouldn't in point of fact you have--it may not be in your waiver guidance, but can we not presume that you have access to that data, or you would require that data?

DR. HACKETT: Yes.

DR. CHAMBERLAND: You're shaking your head "no", and you're saying "yes."

DR. HACKETT: Yes, that's in the information that we look at when a test is first marketed for professional use: sensitivity, specificity, predictive values.

DR. CHAMBERLAND: Can I ask, and is it Dr. Charache, why are you shaking your head "no"?

DR. CHARACHE: Because that was the reason for putting this accuracy consideration into the CDC '95 definitions. It's to emphasize the need to ensure that the sensitivity and specificity and whatever are appropriate to the test that's being considered for waiver.

So I think if there were a preamble to the FDA guidelines that stated that the accuracy would be determined prior to the decision on waiver, I felt that that would handle the issue very well. And then that thing that's now called accuracy would really be called--

DR. CHAMBERLAND: Precision?

DR. CHARACHE: --precision, or whatever you wanted to call it, rather than implying that that was the only accuracy required for waiver.

DR. CHAMBERLAND: So we are in agreement, then, that the data--that FDA requires the data about accuracy? I mean, for a test to come to FDA

for licensure, you have to present the FDA with these data, and it's not that they're missing. They may be missing from the guidance document, you know, mention of that, if you will.

DR. HACKETT: We have the data in the prior application.

DR. NELSON: Yes, Dr. Wilson?

DR. WILSON: Well, the data that are available from the prior application are the data that were used to validate the performance characteristics of the test. What's missing, though, is the next step. If they waive a test, it may be used in a completely different patient setting where the disease prevalence is different, and therefore some of those data probably are no longer applicable because you're not using it in the same setting anymore.

The performance characteristics with a defined set of patient specimens in a certain patient population will be there, but the difference is, in a waived category, is that you're no longer dealing potentially--you may be, but you may not be dealing with the same patient population, so some of the performance characteristics will differ.

DR. HACKETT: The predictive value.

DR. CHAMBERLAND: Predictive value.

DR. NELSON: Exactly, and that may be important. I mean, that's what a patient--

DR. WILSON: Why would you use a separate population?

DR. MACIK: Well, actually that's the same question I had asked. If you have to first of all have 510K clearance of this instrument or test, then that implies a certain amount--that you've already gone through doing your sensitivity, specificity, the whole bit. If you have your 510K clearance, then that tells you whether that test, that instrument, is capable of giving you a result that is the same as another standard in use.

Then the issue that seems to be missing is the step between going from 510K clearance, okay, this is an accurate instrument, and then waiving, to put the waiver on you want to know, can a lay person do it with the same degree of accuracy as professionals can? And then the question is, do we then include in there not just what is the predictive value, etcetera. Do you have some overlay of the clinical significance of a test that also goes into defining the waiver, or not?

And that is, you know, those were kind of the issues basically I was getting at, because the first step with 510K, you have to go through a very stringent criteria. For a home instrument, you have to--the FDA, in order to approve something for a home instrument, you have to show that you had people in the home setting or lay people that did it, before it gets--I believe I'm correct--before the FDA says this can be used at home.

So some of these issues we're talking about, I think if we could maybe get a little bit more feedback from the FDA, what really goes through these tests? What has happened before you hit the waiver part of whether a test has gone?

Because if you've already established the accuracy by 510K, if you've already established that this instrument can be used by lay people at home, to give it its home clearance, then what are we now being asked to look at as far as waiver? Because these are three, you know, really different components, and I think it's something that's very different than the way we think about things most of the time.

DR. HACKETT: These are probably the 25,000 tests that are either high or moderate

complexity.

DR. CHARACHE: I think one of the reasons for wanting to have the accuracy as part of the waiver document is that the definitions of requirements for accuracy are not set at the same level for all types of tests. We heard at CLIAC a couple of weeks ago that the permissiveness for false positives and false negatives, for example for home tests, are set at a very different level than those that are set for other types of tests.

And we know that the sensitivity of some of them, for example, the influenza test that was waived was set at about 63 or 65 percent sensitive. Now, that leaves an awful lot of people who have influenza A and could benefit from drugs, who are not being detected, without necessarily knowing how poor it is in terms of sensitivity.

So it was felt that it would be important to say that the accuracy was tested before the waiver decision was made, but it would also be important to have a knowledge of what the accuracy is under the conditions in which it will be used.

DR. NELSON: Jay?

DR. EPSTEIN: Yes. Well, I wanted to make much the same point. Whereas it's true that the

accuracy is determined in the 510K, it's not true that there is any absolute standard for how accurate that test must be, so that under the FDA guidance it could be a fairly inaccurate test which is nonetheless deemed approvable. But then if it is comparable in what's being called the accuracy study in the guidance, it could in fact become waived.

However, I think it's important to remember that the proposal for HIV rapid tests is that they be no less than 98 percent sensitive and 98 percent specific, where that is the lower limit of the 95 percent confidence interval in a one-sided test. So we are talking about, for HIV rapid tests, tests that have high analytical accuracy. I think that should just--people should bear that in mind when we discuss the HIV rapid tests.

But it is a point of distinction between the CDC scheme in existence on the proposed rule and the FDA guidance. In other words, a test could be waived which is inherently inaccurate, as long as it's no more inaccurate in the untrained hands.

DR. NELSON: Right. Okay, the next presentation--did you have a comment?--the next presentation is the public health strategic goals

for HIV testing. Dr. Onorato from CDC.

DR. ONORATO: Today I am going to discuss the critical role of simple rapid HIV tests in the implementation of CDC's national strategic plan for HIV prevention in the United States.

CDC estimates that there are 800,000 to 900,000 persons in the U.S. who are infected with HIV. We further estimate that 625,000 people know they are infected, while 175,000 to 275,000 persons are unaware of their HIV infection. We think that a substantial proportion of transmission is occurring from persons who do not know they are infected.

There are currently great benefits for HIV-infected persons to know their status. First, there is the benefits of receiving comprehensive HIV treatment and care, especially highly active antiretroviral therapy, or HAART.

There are also significant public health benefits. Several studies have now shown that people who know they are HIV infected make efforts to reduce their high-risk behavior, decreasing the possibility of HIV transmission. The second public health benefit is the potential effect of HAART in reducing the risk of transmission by decreasing

viral load. Thus, knowledge of serostatus can be an effective individual and public health intervention.

In spite of these benefits of knowing one's HIV status, the proportion of persons who receive their HIV test results in CDC-funded counseling and testing programs could be better. These data are from 48 CDC-funded project areas and over 10,000 facilities, including HIV counseling and testing sites; STD clinics; family planning and prenatal clinics; and drug treatment centers. These sites administered about 2 million HIV tests in 1998.

Overall, the test results were received for only 63 percent of HIV positive tests and only 56 percent of HIV negative tests. Among STD clinic clients, who are a very high risk group, only 56 percent of HIV positive and 45 percent of HIV negative clients received their results.

Health departments throughout the U.S. routinely conduct active follow-up to find persons who have had an HIV positive test but who do not return for their test results. Without this considerable expenditure of time and resources that did happen in these situations, these proportions

of persons who know their results would be even lower, and likely are lower for testing in some private settings.

CDC has recently worked with state and local health departments, community leaders, and other federal agencies to develop a national strategic plan for HIV prevention. The overarching goal of the CDC's strategic plan is to reduce the number of new HIV infections in the U.S. by half, from 40,000 to 20,000 infections per year, by the end of 2005.

There are four main goals in the strategic plan. Goal two specifically focuses on increasing knowledge of serostatus. This goal states, "By 2005, through voluntary counseling and testing, increase from 70 percent to 95 percent the proportion of HIV-infected persons in the United States who know they are infected."

Under this goal there are four objectives. First, to increase the motivation of at-risk individuals to know their HIV infection status, and to decrease real and perceived barriers to getting tested. Second, to improve access to voluntary HIV counseling and testing in high seroprevalence communities and in populations at risk.

Third, to increase the number of providers who routinely provide voluntary counseling and testing in high prevalence health care settings, such as STD clinics, as well as in nonclinical and social venues like gay bars or homeless shelters. And, fourth, to increase the percentage of persons who know their results after testing. We think that simple, truly rapid HIV tests will potentially play a significant role in achieving these objectives.

An example is the OraQuick device shown here. The OraQuick test may be used with whole blood from a finger stick, serum, or oral fluid. This test is simple, and requires no mixing of reagents or manipulation of equipment.

The specimen collection is also easy to do. The person being tested swabs his or her gums, using the flat pad end of this device. There is no additional specimen preparation necessary. The swab is then simply placed into a reagent vial.

The results are ready in 20 minutes, and are easy to read, similar to a pregnancy test. The device on the right shows a red line, which is the built-in control, and the specimen in this case is clearly negative. On the left, the device shows

the red control line, and also here a red positive test result. CDC has previously presented data to this meeting showing these tests to be highly sensitive and specific compared to the standard tests.

We believe that rapid tests will be helpful in achieving the public health objectives of increasing knowledge of serostatus. Rapid tests that collect oral fluid or blood by finger stick are easier to implement in community settings, and in some studies they were preferred by clients over venipuncture.

These tests can increase the numbers and types of providers able to offer HIV testing in clinical settings such as ERs and physicians' offices, and in non-traditional settings such as mobile vans and jail. They will also expand access to the highest risk populations, who may reached in social settings such as gay bars, dance clubs, and bath houses which conduct their business after normal business hours. These venues do not have access to a laboratory or to laboratory professionals to perform tests. Rapid tests have the potential to increase the number of people who get their test results, especially if multiple

rapid tests become available.

The potential usefulness of the alternative test collection devices have already been shown in some earlier studies. Although not a rapid test, OraSure, which uses oral fluid for HIV testing, is a simpler and more acceptable method for specimen collection than venipuncture.

In 1997 the Michigan Health Department distributed OraSure kits to community-based organizations that had not previously been able to offer testing using serum-based tests. 12,068 persons were tested in outreach activities, 80 percent by mobile vans standing at street corners and in parks. HIV prevalence was as high, 2 percent, in these settings as in our traditional counseling and testing sites.

Sixty-three percent of persons who were HIV positive returned for their test results when testing was done in the clinic using serum-based tests. In the outreach testing with OraSure, 91 percent of the HIV positives and 77 percent of the negatives received their results.

The acceptability and convenience of testing in a community setting with an oral fluid test improved access to testing, but still many

people did not return to get their test results, including many positives. So in April 1998, CDC recommended the wide use of rapid HIV tests to increase the number of persons who receive their test results without the need to return.

This study was conducted in an STD clinic, and it compared return rates after testing with SUDS, which is the only currently licensed rapid HIV test, and a test of moderate complexity, versus testing with the standard EIA and Western Blot. The SUDS test was performed on-site in the STD clinic lab, and the mean testing time was 22 minutes for negative results and 38 minutes for the positives, due to a need to repeat the test.

One hundred percent of patients tested with SUDS received their tests and their post-test counseling session, compared with only 47 percent of the patients who were positive who were tested with the standard tests.

The rapid testing also appeared to improve entry into HIV care. Eighty-six percent of SUDS-tested patients kept their first scheduled care visit, compared with 70 percent of patients that were tested with standard tests. The mean time to the first clinic visit was 10 days for the SUDS

patients, versus 55 days for standard test patients.

This study showed that tests like SUDS, which is a moderate complexity test but still shortens the time between testing and getting results, were useful in a setting that has clinical laboratory support on-site, and may also improve getting positive persons into care. However, the definition of "on-site" turned out to be important.

Investigators at Grady Memorial Hospital in Atlanta found that two-thirds of patients who were newly diagnosed with full-blown AIDS had come to medical care but had not received an HIV test in the 12 months prior to their AIDS admission. These patients had had a median of four patient visits, mostly to the Grady ER and Urgent Care Center, without receiving an HIV test.

So, in response, Grady conducted a study where clinicians were encouraged to recommend HIV testing routinely to all patients in the ER and the urgent care setting who were age 16 to 65 years. Compared to the same time period in the previous year, 1,687 more patients received an HIV test, and 27 new HIV infections were picked up. More patients had a CD4 count greater than 200, which

suggested that these patients were also being picked up at an earlier stage of disease.

This study will be published in next week's MMWR, which is occurring just before National HIV Testing Day on June 27th, and will show the impact of routinely recommending HIV testing in clinical settings with high seroprevalence.

All the testing was done in the Grady Hospital laboratory, and SUDS was used as the rapid test. The mean time to getting the test results was two-and-a-half hours, so only 29 percent of patients tested with SUDS received their results the same day. So even though a rapid test was used, the need to perform this particular rapid test in the hospital laboratory rather than in the clinic or the ER, required almost all patients to return for a second visit to get their results, or required an active follow-up by the physician's assistant, which was a great burden on the busy Urgent Care Clinic.

Another ER study illustrates the consequences of even an hour's delay in getting back test results. In this case, SUDS was performed either in the main hospital lab or in a

special satellite lab set up next to the ER. When SUDS was performed in the main hospital lab, it required a mean of 107 minutes to get test results back, compared with the satellite lab which reduced the delay to 48 minutes. Only 45 percent of those tested in the main hospital lab received their results before leaving the ER, compared with 80 percent of those tested in the satellite lab.

Thus, tests which require a moderate complexity lab can cause enough delay to reduce the number of patients who can get their results, and for settings not directly affiliated next to a lab or near a lab, such as community-based organizations or outreach vans or a private physician's office, these delays are anticipated to be much greater, and may negate the advantages of using a rapid test. Ideally, if multiple rapid tests become available, clients will receive their test results, including confirmatory results, in one visit, eliminating any of the loss to follow-up that now occurs.

We and many others are concerned about appropriate counseling for persons receiving rapid tests. Public health settings where SUDS tests have been used, have been experienced now in

counseling clients with rapid tests, and these techniques have been published in the peer review literature and on the CDC web site.

CDC publishes the PHS guidelines for HIV counseling, testing and referral, and later this year the new version of these guidelines will address counseling for rapid tests. CDC recommends that before rapid testing is done, that clients be informed that confirmatory testing will be necessary if a rapid test is reactive.

If the rapid test is negative, the client may be told that he is not infected, unless there has been recent risk exposure, in which case the client is counseled to return for retesting after an appropriate time interval.

If the rapid test is reactive, the counselor arranges confirmatory testing and discusses what the patient may want to say to his partners. The counselor will also recommend that the client adopt various behaviors to reduce the risk of transmission while waiting for the confirmatory test result. This type of counseling may actually decrease the risk of transmission to partners sooner than when using standard testing.

Several studies have shown that people who

receive a preliminary reactive rapid test result will return for a confirmatory result. The first set of bars on this graph shows the return rates for persons testing in that ER study that I showed before, whose HIV test was positive. In this case, three attempts were made by phone and letter to reach all persons who did not come back. With this active follow-up, 62 percent of HIV positive patients who had standard testing returned for their results, compared to 73 percent of the patients tested with SUDS.

In the STD clinic study, which is shown here, only 45 percent of HIV positive patients tested with standard tests returned to the clinic on their own, compared to 94 percent of patients who had been told that their SUDS result was reactive. After follow-up by the local health department of non-returnees, a total of 79 percent of HIV positive patients tested with standard tests received their results, compared to 97 percent of the SUDS patients who had a preliminary reactive result.

So what is the best way to implement the use of rapid tests? A number of questions need to be addressed, including training, quality

assurance, and precision. The CDC laboratory is planning to conduct studies with well characterized specimens to compare results of rapid testing done by laboratory professionals and lay users. CDC has also funded four sites to do operational research in settings where these tests will be used by individuals who represent the anticipated users.

If rapid tests become available, CDC and other PHS agencies, state and local health departments, and community leaders will then develop algorithms for their use, so that test results, including confirmatory test results, would be available in only one visit.

As stated, the PHS/CDC guidelines for counseling, testing and referral provide recommendations for all aspects of the testing process, and these will be updated as multiple rapid tests become available. In addition, states have laws or regulations that govern persons authorized to order rapid tests and give rapid test results, and that govern the processes of consent, counseling and laboratory testing. CDC will work closely with health departments and policy-makers to ensure that apprcpriate practices are in place when and where rapid tests are used.

Rapid tests are a valuable and long-awaited technology which is widely available in many parts of the world, but not in the United States. Simple, truly rapid tests have the potential to greatly expand HIV counseling and testing services to community settings and physicians' offices who do not have the ability to use more complex tests. By substantially reducing the time to perform an HIV test and eliminating the need to return for a second test, the number of persons who know their results will increase.

The greatest potential of rapid tests to contribute to both the health of HIV-infected individuals and our public health goals of stopping this epidemic might be realized if they are made widely available and eligible to be considered for CLIA waiver. Decisions can then be made based on data as it becomes available from planned CDC and other studies.

If you haven't seen any of these rapid tests, I'm just going to pass around, these are tests, one is a negative test, one is a positive test, done using the OraQuick collection device, test device.

DR. NELSON: Thank you very much.

DR. ONORATO: And I'll take questions.

DR. NELSON: Are there other questions? Jeanne?

DR. LINDEN: Are you assuming that point-of-care testing will only be done if waived?

DR. ONORATO: We are not assuming it will only be done, because point-of-care testing in a sense is done using OraSure and SUDS, but the complexities around needing to, in one case, get a test, a specimen to a laboratory to test, really greatly delays getting the results back to people and, as I've shown, greatly affects the follow-up rate and the rate of people getting their results back when they're tested. So while point-of-care testing in a sense is done now, the problem becomes getting the results to people.

DR. NELSON: Dr. Charache?

DR. LINDEN: Well, but you seem to be assuming that the testing cannot be--that there can't be remote moderately complex labs at the point of care, and certainly there are.

DR. ONORATO: That would be possible, but for the kinds of groups and places that we're talking about, which is outreach, homeless shelters, it's very unlikely that they are going to

be able to set up moderately complex laboratories.

DR. LINDEN: Right. For the social settings, I would agree. For the medical care settings, I don't think that's the case.

DR. CHARACHE: Dr. Onorato, I think, for the reasons you have presented and additional ones, we can very strongly support the need for tests that are rapid and accurate and can be done in a wide range of sites. A waived test is only one of the mechanisms through which this can be accomplished. Does CDC care what the mechanism is, if there are other ways of having a test that can be done in your bath houses in a rapid way by someone who is less trained? In other words, under the supervision of a moderate or high complexity lab, but not on site at the time, with provisions for permitting. So do you care that the test has to be waived, or are you after the goal of the on-site, rapid, accurate test?

DR. ONORATO: We would certainly like to see tests done at the time that the client or the bath house attendee is actually standing there, and before they can leave that setting, will get their test results.

DR. CHARACHE: So as long as that happens,

you don't care whether it's waived or not waived?

DR. ONORATO: If there are other ways to do that than a waiver, that would certainly be appropriate, but we are trying to maximize as much as possible all the various places where we can reach people.

DR. CHARACHE: Right.

DR. SCHMIDT: In setting this up, maybe a helpful caution. There are various state laws, as I'm sure you are aware, which define a "professional," and so you've got the medical technologist versus the medical technician. The medical technician is very qualified, but if you write it in such a way, you will run into local problems. In other words, differentiating the lay person from the professional is a little sticky. What's professional?

DR. ONORATO: Well, in fact, you raised a very important point, that in fact HIV counseling and testing is regulated under state laws and regulations in every state, and so in fact the restrictions on who can give results and do tests and various other things are state-by-state, and not necessarily the same in every state. And certainly we would work, we would have to work

state-by-state with everyone, and would have to plan to do that. And that is, in fact, an additional safeguard where rapid tests could be used.

DR. NELSON: Okay. Thanks.

Next speaker is Dr. Judith Yost from HCFA, requirements for moderate complexity tests and the HCFA experience with CLIA waived tests in the laboratory.

MS. YOST: I thank you for the extra degree, but that's okay.

DR. NELSON: Oh, that's okay.

MS. YOST: Good afternoon, everyone. I'll take it. We can go ahead.

I'm going to give you some background, which you've already seen several times today, but I think it's important in these conversations that, again, the CLIA law states that waived tests are simple and have an insignificant risk of an erroneous result. Waived tests currently, under the regulations for CLIA, have no standards or routine oversight.

Right now in the country we have 170,000 laboratories enrolled in the CLIA program. They range from schools and ambulances all the way to

large reference laboratories and hospitals, so we have the whole gamut. Out of that 170,000, 92,000 are already waived laboratories, so that's the context at least from which we're coming.

My talk today is actually two parts. I'm going to talk to you about the HCFA experience with waived tests over the last nine years or so, as well as talk to you a little bit about the moderate complexity requirements so that you have a basis for comparison.

Again, as further background, there is some authority however within CLIA, that if there is a problem in a waived laboratory, we still can go visit that laboratory. If the lab is perhaps performing a moderate complexity test and only has a waived certificate, we can visit, or if there is a complaint about possible risk of harm, we can certainly go visit that laboratory, as well.

There is one requirement currently under CLIA for those laboratories, and this is something you have to remember throughout this talk, is that waived laboratories must follow the manufacturer's instructions.

As additional background, several of the states that work with us as part of the CLIA

program did some investigational studies of waived laboratories, because they had a large number of complaints and they were concerned about the large number of tests that were being waived. They went into, on an educational basis, they went into several hundred laboratories in 1999 and 2000. Of the laboratories they visited, 50 percent of the labs they visited had quality problems. The majority of those were not following the manufacturer's instructions.

Also, the Office of the Inspector General, after hearing of the findings of the state problems, also did some investigation of waived laboratories, as well. Their findings were very similar to the previous ones. CDC also had some cooperative agreements with several states and did concurrent studies, and they too found essentially 50 percent of the laboratories with quality problems.

Because of those findings, the seriousness of those findings and the concern about quality, because that clearly is the intention of the CLIA requirements, HCFA expanded the studies that had been initially done to eight more states, in which we took a 2.5 percent sample of the waived

laboratories in those states and visited those laboratories. We did announced visits. They were educational and information-gathering, just to find out what in fact was going on in those laboratories, and I'll be telling you some examples of some of the things we found, because I think that helps bring it home.

Let's talk about the findings. What did we find, because I'm sure you're waiting to hear that. Okay. The people who primarily do waived testing right now are nurses, physicians, LPNs, and medical assistants.

Some of the problems we identified were that 32 percent of the waived laboratories we visited failed to have current manufacturer's instructions, so we don't know what they were doing but they sure didn't have the directions. And additional 32 did not perform the quality control that was required by the manufacturer's instructions or CDC's instructions per waiver.

Sixteen percent failed to follow the current manufacturer's instructions. I'll give you an example about following manufacturer's instructions. The rapid Strep A test is a very simple test. It has two reagents, A and B, and you

need to add them to the test in that order, A, then B. We found a laboratory that was, for some reason, adding the reagents in reverse order and never had a positive test. And we all know the implications of a false negative Strep test, Strep A test. So that's one example of something we did see.

Seven percent not performing calibration per the manufacturer's instructions, and maintenance per the manufacturer's instructions. We actually have a state that reported a death in a nursing home because they did not perform the appropriate calibration and maintenance on a glucose meter, and the patient, because of an inaccurate result, did die.

Twenty percent of the laboratories were cutting occult blood cards and urine dip sticks. In relation to that, we also found a facility that was using the sticks for a glucose meter upside down. Additionally, we found that personnel that were performing the tests were neither trained nor evaluated at any point.

One of the things we found as part of that personnel issue was that the people who were training them were people who were trained by

somebody else, were trained by somebody else. So you know in history that whole idea of "whisper down the valley" doesn't always bring you to the exact same information.

In addition to that, exacerbating the situation, is the high turnover in very small facilities. When you visit them, from one time to the next, even the laboratories that we routinely survey, there is a new person there doing the testing, you know, different from the person from the last time you had visited, so it is a concern.

Again, storage instructions aren't being followed. Laboratories using expired reagents. I have a case, I actually had an attorney call a couple weeks ago about a laboratory that was using expired reagents for occult blood testing, and had a patient who could point to a delay in a diagnosis of GI cancer as a result of that use of expired reagents, so these are real situations.

To give you some background on the OIG study, the OIG study had very similar findings. I'm not going to enumerate them. One thing we did not look at, however, was the failure to identify correct results, which was something they did find. We did not evaluate for that, so I don't have data

on that, but they did find a significant amount of that. And part of the concern is that, regarding some of the waived tests, is that there's no way you know that the answer is wrong.

Just some background, just some statistics from that study. Again, to summarize. 270 laboratories. They consisted of physician office labs, skilled nursing facilities, and end stage renal disease facilities, so it was kind of a proportion, a very good correlation to the actual population of laboratories in the country, because that's pretty representative. Also, there were again urban and rural. There were also laboratories both in states that have laboratory licensure programs and some without.

What did we do as a result of that, or what are we going to recommend? Several things. First and foremost, education, because we feel that part of the difficulty that we saw was, these folks really just didn't know what to do with these tests.

And so education is the first and most important thing that we're going to work on. We're going to work with CDC in developing a comprehensive program. We'll work with the

approved accrediting organizations, with the AMA, with the manufacturers and others, to develop a comprehensive program for these labs. We also may look at--we haven't decided for sure--we may look at a percentage of those laboratories, as well.

We also are considering a self-assessment tool for those laboratories, with a quality control or quality assurance focus, just to give them some idea in writing about what they might do to ensure the quality of their testing. With the application process for the CLIA program, we will provide additional information on the application and probably on our web site, as well. We will probably call some of those laboratories just to see if they have any questions or problems that we can assist with. With those recommendations, we are planning a comprehensive plan that will involve a sequential implementation, dependent upon resources and funding for the program.

We have some additional recommendations from the Office of the Inspector General, including collecting the test menus of the laboratories. That, we need to obviously evaluate, due to the added burden that might cause. Also, because of Medicare payment, there are concerns of

laboratories billing for tests that they are not authorized to perform.

So, in summary, let me tell you where we are. The study that we conducted does corroborate the findings of the previous studies, very, very closely, that 48 percent of the laboratories have quality testing problems. That includes not following manufacturer's instructions and not performing required quality control. It also indicates that physicians and nurses who are performing these tests are not following the manufacturer's instructions.

Laboratories that are located in states with regulations seem to have a lot fewer problems. I looked at the data again this morning, and it appears that non-regulated states have four to eight times greater problems than those that are in regulated states.

One of the messages I wanted to send, however, was those labs that we visited clearly wanted to do a good job, just did not have the information to do so. The laboratories were actually appreciative of the information they received. I mean, all of them weren't jumping up and down when we arrived at the door, but clearly

did feel that the visit was educational and information.

The number of waived laboratories does continue to increase, because the number of waived tests increases, so more and more tests are waived, more laboratories have that opportunity.

CLIA-regulated laboratories demonstratedly have very good data that shows that the laboratories that have been regulated actually had the same problems. When they started out, they didn't follow the manufacturer's instructions, either. But over time we have seen a significant improvement, greater than 75 percent improvement over the course of the program.

We also feel that there are significant findings in this study--and that's the key thing, and that has very serious implications for patients--incorrect results because of not following manufacturer's instructions, and the fact that the testing personnel are not trained, so it's a combination of that that gives us that potential for harm. Again, several folks have all said the same thing, that the experts agree that there is potential of harm if any test is performed incorrectly.

We clearly support the development and use of rapid tests, regardless of what they are, and particularly point-of-care testing, realizing that that's the way to get to the patient population that needs the appropriate care.

Just as a final note, I wanted to say that a lot of skeptics say to us, "Well, you're just telling us about noncompliance of the laboratory to requirements." No, we're not. I think we have enough examples, we are beginning to collect very pertinent outcome information that the performance of tests incorrectly, regardless of how simple, can lead to dire patient outcomes. I gave you some examples, but we are collecting that, so that does exist.

Okay, let's go to the second half of this talk, and this is to kind of demystify some of the perceptions. I think we talked about perception before, about a perceived barrier. Let's try and clarify some of that, as far as moderate complexity.

To enroll in the CLIA program, you need to complete an application, not a hard thing. It's four pages long. You can find it on our web site, which is www.hcfa.gov, click on "laboratories" and

you're there. Complete the application, whether or not you want to be waived or whether you want to be moderate complexity.

For waived laboratories, you enroll in the program by completing the application. You need to pay a certificate fee every two years of $150. You need to follow the manufacturer's instructions. Well, we all know nobody does that anyway.

One of the points I wanted to make today was that once the test is waived, regardless of whatever professional category or intended use it may have been approved for, it can be done in any place by anyone. For some people that might be a good thing, but for others we can talk about the potential risk.

An example that we have seen is that glucose meters that are approved for basically screening are being used in the field now, because they are waived, for glucose tolerance testing. We're not sure--and that is obviously a diagnostic procedure.

Okay, let's go on to moderate complexity requirements. As far as the requirements, they are the same as far as certificates as they are for waived. The waived laboratories need to have one

certificate per site of testing. CLIA regulates the site where the test is performed, and that's the same, so one certificate per site.

However, there are some exceptions that I was asked to tell you about, and I actually thought of some more while I was sitting waiting to get up today. One of the key ones I think that might be applicable for this situation is the limited public health option. This is more an entity that has multiple sites. If it's a state agency that has a state laboratory or a government facility that has multiple sites, they can avail themselves of this single certificate for all those sites rather than a certificate for every site, as others would have to do.

All you need to do is meet the three simple criteria that are outlined here. You need to be a federal, state, or local public health laboratory or a not-for-profit laboratory. You need to perform any combination of 15 waived and moderate complexity tests. That's your choice as far as the combination. And you can have as many sites as you want to under that certificate. There is no limit of sites. There is no limit of volume of tests that you can perform. It's just that all

sites need to do the same 15 tests, so if you have 10 sites, they all can't do 15 different tests. They've all got to be the same.

So what happens with that is that the one certificate just costs you that fee every two years, as well as the survey, and we'll talk about later the proficiency testing, which will also be a limited cost because it's by certificate.

There are also some other options available under the CLIA regulations the same way for multiple testing sites. One is called a temporary testing site. That can be anything. It can be the drug store, the grocery store. It can be the bath house. It can be wherever. It's called a temporary testing site. Multiple sites can be aggregated under one certificate to meet that.

There is also an option for a mobile van, and that's another possibility, where vans would travel through the streets to do testing in the van. That also has that same exception allowed, not even a limited public health. That can be just one certificate. That's under, say, like a hospital that had a mobile van on the street. They only need to have the one certificate.

The moderate complexity laboratories--we need to go back--

DR. NELSON: I wonder if you could summarize the important points that you haven't covered? We have 11 people that have asked to come, and we are now about an hour or an hour and a half behind, and there are people that need to catch planes and so. So I'm happy to go until midnight, but I think those who have a plane at 6:00 or 7:00 might have a problem. I'm sorry to do this, but if you could abbreviate the rest of your-

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MS. YOST: I will do my best.

Moderate complexity laboratories do need to be surveyed every two years. Again, for low volume laboratories we have bargain fees available. They would pay, for a certificate and a survey, a combination of $450 for 4,000 tests every two years, and that comes out to be 11 cents per test, so I don't think that's too bad. Our surveys are educational, they are not punitive, and those laboratories that are good performers are allowed to do a self-assessment on alternate sites, so that we actually don't go visit them if they're doing a good job.

In addition, the laboratory director qualifications, the minimum for moderate complexity is a Bachelor's degree in a science with some experience in the laboratory, so we're not--I don't think that those minimum requirements are unmeetable. So that means that even doctors could be directors of these laboratories. Testing personnel is high school degree with training in the laboratory as the minimum.

There are quality control requirements but, interestingly enough, they are about the same as they are for waived tests, two levels of control per day of testing, and built-in controls are acceptable. For your manual, you can use the package insert, and that's the same thing as the manufacturer's instructions for the waiver.

For proficiency tests, you need to enroll with the vendor of your choice, and you only need to enroll for the tests that you do. Proficiency testing has proven to be quite educational to the laboratory. We have data that indicates that as the laboratory does proficiency testing, they learn how to improve their performance.

That Strep A example I gave you, about the laboratory that did the test reagents in reverse,

that's how they found out about their problem. Before the test was waived, they were in proficiency testing and they failed, and that's how they figured out they had a problem, so there is truly a value there.

Again, with proficiency testing, under the limited public health they only need to enroll once in proficiency testing for that certificate. There is a patient test management requirement, which all that is, is a record-keeping system. You can use the patient chart. You have no required forms for your orders or for your results.

As far as quality assurance, basically all that is, is wrapping up everything that we already said. It's all the quality requirements. We want to be sure that you communicate with your patients and your clients, that you solve problems, that you look at your lab data to make sure it correlates to patient information if you have it. So it's essentially the things that you're already doing in your facility to ensure quality.

And, last but not least, there's only a minimum amount of enforcement taken under CLIA, because we are educational.

As far as the summary--no, one more--as

far as the summary--I'll keep talking so we don't take up the time--again, we support the development of rapid testing. However, we want to ensure that it is done in a quality environment, because no patient can--we all know that an inaccurate test is of no value to a patient.

CLIA standards for moderate complexity are minimal, they are basic, and they are flexible. They are low cost and low burden. You can use existing mechanisms. We have state agencies that provide technical assistance. We have very strong evidence that accredited laboratories and state-regulated laboratories doing waived tests have no difficulty meeting moderate complexity standards. The example, a good one, is the ancillary sites in a hospital facility or their clinics.

Nine years of CLIA have demonstrated no loss of access. In fact, the number of physician office laboratories enrolled has increased over the years, and 25 percent of them are still moderate complexity and doing quite well. I learned from a seminar I teach at at Wake Forest that the number of physicians going to moderate complexity is actually increasing over time, because they have found it not to be onerous at all. Lab performance

as well over the nine years has also improved.

So, again, a waived test can be done in any place by any person, regardless of its intended use, with no medical intervention. So it's important, in the case of a rapid HIV test which has huge pre- and post-testing ethical and social implications, that the test is performed correctly.

Thank you.

DR. NELSON: Thank you very much.

Comments? Yes, Mary?

DR. CHAMBERLAND: Can I ask a question?

MS. YOST: Yes. I'm not going home yet.

DR. CHAMBERLAND: Just a quick question. I'm sorry, I just didn't quite catch what you said about--when you were talking about limited public health option, you mentioned temporary--something that was not on your slide. Temporary sites?

MS. YOST: Temporary testing site is another option you can take. The limited public health is on option. Temporary testing site is a second. And the mobile van is actually a third. So all of those, and actually the mobile van and the temporary testing can be rolled into one certificate, if there are a bunch of them, at no extra cost.

DR. CHAMBERLAND: Again, envisioning some of the public health outreach settings like bath houses, etcetera--

MS. YOST: Right. Yes. Exactly.

DR. CHAMBERLAND: --a bath house could apply as a temporary--

MS. YOST: Temporary testing site.

DR. CHAMBERLAND: --testing site of moderate complexity? That would be moderate complexity?

MS. YOST: Yes.

DR. NELSON: Thank you.

DR. CHARACHE: Just to clarify, one of the questions I asked the previous speaker was that if there is the ability to have a rapid accurate test with real on-site, including bath houses, that was not waived, would this answer the need? And so now I think you're saying that yes, that can be done under the moderate complexity by trained high school graduates.

MS. YOST: Yes.

DR. CHARACHE: Thank you.

DR. MITCHELL: I had another question.

DR. NELSON: Go ahead.

DR. MITCHELL: So if somebody is licensed

under the public health, can they also--does that also include the outreach types of activities that you talked about?

MS. YOST: Can be, yes.

DR. MITCHELL: Okay, so they would not require a separate temporary?

MS. YOST: No. If you meet that definition, you can use that for all your sites, regardless.

DR. MITCHELL: Okay. Thank you.

MS. YOST: You know, I would hope that you don't include the whole country, but it clearly--

DR. CHAMBERLAND: Let me get a clarification. If I understand this correctly, a health department, local or state, would have to be willing to take on the responsibility, in a limited public health certificate, of supervising, if you will, these satellite point-of-use places, be it a bath house--

MS. YOST: Yes. The laboratory director will be responsible.

DR. CHAMBERLAND: I guess that's another question for discussion, as to how many would be willing to do that, or if that's a routine thing or not.

DR. NELSON: Blaine?

DR. HOLLINGER: You said that 48 percent of the waived labs had testing, quality testing problems. What percentage of moderately complex laboratories, that have caps and so on, had perceived deficiencies as well? It's very high in those as well.

MS. YOST: I can only speak to the laboratories that HCFA surveys. Currently, I think it's about 11 percent. It started out at 35 percent were not following the manufacturer's instructions. It's down to about 11 over the last six years.

DR. NELSON: Yes?

DR. JACOBS: I have a question. You mentioned that in nine years there has been demonstrated no loss of access, and Dr. Onorato spoke about some of their measures of access to test results. Could you tell us how that was evaluated by HCFA?

MS. YOST: Basically, it was not a scientific study by any means, but we do have, HCFA has regional offices across the country that are responsible for a number of states in the program. And we always, we just do a periodic check with

them to determine whether or not there is testing available.

Now, I realize that testing in a site that may be comfortable, versus having to have a specimen collected and transported to another site to be performed, are different, but it still is access. It is available. I can tell you that any reference lab in the country will take their plane and go to any little two-bit town to pick up a specimen, you know, if they need to, so it is not a problem. There is access available.

We also see the number of physician office laboratories, which is the ideal situation where you have a physician ordering, performing the test, determining treatment at the same time, and then allowing the patient to go home without having to return, we see that number going up over time. We had about 89,000 enrolled in the program in 1992. There are now 96,000 physician offices enrolled in the program.

DR. NELSON: Okay, make it brief.

DR. SIMON: Just a quickie on, just because I think this issue of how complex is moderate, when you say director's qualifications, BS in science, I just think the committee should

realize that person has to have some special qualifications. I know they can get it through this seminar you mentioned at Wake Forest, or training. It just can't be anyone who has a BS degree. It has to be laboratory medicine.

MS. YOST: No, I said experience and training. Yes, I mean to be fair.

DR. NELSON: Can't be a B.S. in Latin or something like that.

DR. SIMON: Typically they're M.D.'s.

DR. NELSON: Yes. Okay, thank you.

Now, back to Dr. Cowan, who is going to give us the perspectives of the FDA and the questions for the committee, which I think is important.

DR. COWAN: I'm going to make this very brief. I only have about three slides. In fact--

DR. NELSON: And I hope you don't have eight questions, maybe just a couple.

[Laughter.]

DR. COWAN: That, I don't think I have control over. Oh, questions for you?

DR. NELSON: For the committee.

DR. COWAN: Oh, I'm sorry. I thought questions from you.

access to outreach settings through public health agencies or nonprofits, and may also provide the desired oversight for testing.

What we are ultimately after here is availability with oversight. I didn't list the other two options that Judy Yost described earlier. I wasn't aware of them myself. But those are also open to consideration, the temporary site and the mobile van, as well.

So, just to reiterate the questions for the committee, Number 1: Considering the known benefits and risks of rapid HIV testing, should FDA consider the possibility of removing all CLIA quality assurance oversight for such tests, that is, waive simple and accurate HIV testing from CLIA under its proposed criteria?

I put "under its proposed criteria" bolded, just to remind you that we are talking here about the draft FDA guidance.

Secondly, if not, what are the criteria that should be applied in making waiver decisions for these tests? In other words, is there something special about a rapid HIV test that we should consider when considering waiver for these things?

And, finally, if rapid HIV tests are not waived, is it appropriate to pursue other approaches under CLIA, for example, limited public health use, temporary site, mobile van, to promote wider access to rapid HIV testing?

DR. NELSON: Thank you. They're not yes or no questions, but I think it gives us a background for what we have to decide, and that was helpful.

I would like to now move to the people that have asked, people and organizations that have asked to make a statement, and if any of you have a plane that leaves at 4:30, well, you're not going to make it. But if you have one that leaves even a little later--and Dr. Susan Rosoff does have a plane, and so I'll let her talk first. And again, if you could keep your comments to five minutes, realizing that there are 11 people that have requested.

OPEN PUBLIC DISCUSSION

DR. ROSOFF: Thank you. It's a train, but thank you.

DR. NELSON: Okay.

DR. ROSOFF: Dr. Nelson, members of the committee, I'm currently the Director of

Transfusion Medicine at the Virginia Commonwealth University Health Systems in Richmond, Virginia, and I'm here today as a representative of the American Society of Clinical Pathologists or ASCP. ASCP is a nonprofit medical specialty society, organized for educational and scientific purposes. Our 75,000 members include board-certified pathologists, other physicians, clinical scientists, and certified technologists and technicians.

We agree with many of the individuals here today that testing for HIV should be accessible to the general public. Laboratory tests are an essential component of programs for the accurate diagnosis of HIV that lead to prompt treatment and prevent its future spread. However, as a leading medical organization devoted to the application of quality laboratory testing, ASCP has serious concerns about the potential waived categorization of rapid HIV antibody screening.

First, the rapid HIV antibody screening test has a lower specificity and sensitivity than the enzyme linked immunoabsorbent assay tests. As an example, 98 percent might sound like a very good specificity for a rapid HIV test, but

unfortunately, if this test is used in members of the population with low prevalence, such as normal healthy blood donors, most of the people who get a positive result are actually getting the wrong result.

As an example, and I hope you can bear with me with the math, the prevalence of HIV in U.S. women is 115 per 1 million. Of these 1 million women, therefore, the remaining 999,885 will not have HIV. Yet, with a specificity of 98 percent, 19,998 of these women will get a positive test result without disease. Of the 115 women who have HIV, two of them will get a negative result even though they do have disease. Therefore, of the 1 million women tested, more than 20,000 will get a positive test result, but the positive test result will be wrong in 99.4 percent of the time.

According to the Clinical Laboratory Improvement Amendments of 1988, waived tests must employ methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible. If the rapid HIV test is not accurate, patients may be harmed, first of all by getting a false positive and being treated pharmacologically even though they do not

have disease, in addition of course to the psychological and emotional harm that is incurred by a patient who gets a false positive result.

On the other hand, a person with HIV who gets a false negative result may not seek further testing or treatment, having a tremendous impact on their future health. False reassurance of a negative response is detrimental, as infection may spread and cause further public health concerns. And there is also a concern that there are certain people at higher risk of disease who may enter the blood supply as a result.

Second, according to CLIA regulations, laboratories performing waived tests must register as such, and as we have just heard, are required to follow manufacturer's instructions. And also as we just heard, the recent survey done showed that 48 percent of waived laboratories had quality test problems. With a test as critical as HIV, screening should not be subject to the same practices.

It's also important to note that the CLIA waived category does not provide a mechanism to assure pre- and post-analytic interventions, yet this is a significant part of HIV testing. One

concern, of course, are proper personnel available to interpret results? If performed in a clinic setting, will you be able to get a patient to come back for the necessary confirmatory testing?

From my experiences, too, having worked in a blood center, there might be an interest in using a test like this on a blood drive to rapidly assess a donor's eligibility. I can only imagine going to a Sunday service and having a whole group of people come up and get tested, and having parishioners walk away crying and screaming, wondering what their neighbors think and wondering what their test means. Again, that would be a very low prevalence group of blood donors and would have a lot of false positive test results.

In addition, some people may not be aware that physicians are not always on site at a blood donor center, and therefore there would not be people necessarily available for counseling. Using a waived test in this setting, therefore, could lead to profound consequences.

Finally, there are also concerns about public health reporting of a positive HIV test. With the use of a waived test in a setting that does not typically require public health reporting,

it will be difficult to assure the reporting of this information.

Again, on behalf of the ASCP, we deeply appreciate the importance of HIV testing, but urge the committee not to recommend rapid HIV antibody testing for waived categorization. Thank you for the opportunity to express these views before my train leaves.

DR. NELSON: Okay. Yes, Mary?

DR. CHAMBERLAND: I think we need to get a very clear clarification. It is not the intent to use the rapid assays in a blood donation setting, correct?

DR. EPSTEIN: We have historically approved two HIV rapid assays, of which only one is still on the market. In both of those cases, the company was able to show that with proper oversight, those tests did perform with sensitivity and specificity equivalent to the conventional EIA, and we did approve them for use in settings, including donor screening, where a routine EIA was either not available or not practical.

So, you know, there are occasional situations, for example where you need an HLA matched platelet donor, you have to have the

platelets in a few hours, you don't have enough time for the turnaround time at the lab, we have indeed permitted licensed rapid tests to be used as donor screens. However, we have never approved them as routine donor screens.

DR. CHAMBERLAND: I guess the second thing I wanted a clarification on is the example that you gave about sensitivity and specificity. It's just an inherent characteristic of the test, and using it in a low prevalence population, you know, what we're running into here are predictive value problems, and that would happen irregardless of whether it was performed in a waived setting or in a moderate complexity laboratory setting, if the test is performed the way it should be, according to manufacturer's instructions, whatever. So the setting shouldn't impact, all things equal, what the predictive value of the test is, correct?

DR. ROSOFF: But if the specificity is lower than the test that is available, if there's a 98 specificity, I think sometimes when you hear 98 specificity, that sounds wonderful. But the current test, for instance, that we use in our hospital has a 99.9 percent specificity. So that translates to 20,000 people. It's not--

DR. CHAMBERLAND: Right. But what you're talking about that is just your concerns about the sensitivity, specificity of rapid tests per se, which is separate from the setting, you know, the waiver/non-waiver question.

DR. ROSOFF: Yes, but I guess, too, when you're using it with less experienced personnel or personnel not around to help counsel people at that site, then that may have different implications from a test that is more accurate, let's say.

DR. CHARACHE: Further clarification on the issue of the use of rapid tests versus the waived tests for blood products. Is a waived test--once a test has been approved by the FDA, it's my understanding that there is no control over what is called "off label" use. So if a waived test is intended for diagnostics in a high prevalence population, it doesn't mean that it won't be used in a low prevalence population, such as women ready to deliver babies, or used for blood or blood products. There's no limitation in terms of the law on waived tests.

Is there a second law or rule by the FDA which says that off-label usage of such a product would not be or is not permitted without review by

CBER for blood product usage? That would be an added requirement.

DR. NELSON: While Jay goes there, I don't think it would be acceptable to the FDA as a screening for blood donors. That is--in other words, you could use it, but you would also have to use the more sensitive test. Isn't that right?

DR. CHARACHE: But is that the law?

DR. EPSTEIN: Well, yes, we dually regulate the blood centers. We regulate the product but we also regulate the operational procedures. So indeed we do require that blood establishments follow manufacturer's product inserts and use products only as appropriate labeled, unless they have obtained exemptions. So we are in fact closely regulating the use of tests in the blood screening environment. Now, with respect to medical use of diagnostics in general, I could not say the same thing.

DR. CHARACHE: Thank you very much.

DR. NELSON: Okay, if there are no further questions, let's move on to Chris Aldrich, National Alliance of State and Territorial AIDS Directors. Again, if you could be succinct.

MR. ALDRICH: Good afternoon. Again, my

name is Chris Aldrich. I am the Prevention and Care Programs Specialist for the National Alliance of State and Territorial AIDS Directors. I want to thank the committee for the time today to present comments. These are the comments from Mark Loveless of Oregon, who is currently the AIDS Director for Oregon and the NASTAD Chair, and Julie Scofield, the Executive Director of NASTAD. These comments are made on behalf of the membership of NASTAD.

So, on behalf of the National Alliance of State and Territorial AIDS Directors, we are writing to request that rapid testing be eligible for a waiver under the Clinical Laboratory Improvement Act to allow administration of rapid HIV tests in non-clinical settings by trained staff other than certified laboratory personnel.

NASTAD represents the chief health agency staff that has programmatic responsibility for administering HIV/AIDS health care, prevention, education, and supportive services funded by state and federal governments. NASTAD seeks to promote effective national, state and local responses to the HIV/AIDS epidemic, and has considerable expertise in identifying community needs and

meeting the challenges of the HIV epidemic nationwide.

The Centers for Disease Control and Prevention estimates up to 900,000 people in the United States are HIV infected. However, of those infected, up to 275,000 are unaware of their serostatus. Early identification of HIV infection provides numerous benefits, including improved health outcomes, access to support services, and a decrease in risk-taking behaviors, reducing the likelihood of further transmission.

CDC has adopted, as one of the goals of its HIV Prevention Strategic Plan Through 2005, increasing the percentage of HIV-infected people that know their serostatus from approximately 70 percent to 95 percent. In addition, the Ryan White Care Act Amendments of 2000 require states to develop strategies for identifying HIV-infected individuals and linking them with comprehensive prevention and care services.

Health departments support counseling, testing, and referral--CTR--activities in a broad range of clinical and community-based venues. Providing outreach CTR services in communities with high HIV prevalence through social service

agencies, mobile vans, and social venues has become a key strategy in ensuring access to CTR services among individuals at increased risk for HIV infection.

Many individuals that elect to be tested in these settings would not otherwise seek testing. Outreach CTR services not only provide more convenient access within a high-risk community, but also allow testing to be offered through trusted providers, a critical issue for communities of color disproportionately impacted by HIV. Health departments have placed emphasis on ensuring provision of high quality services through investment in training, evaluation, and quality management programs.

However, a challenge faced by CTR programs regardless of setting is ensuring that clients counseled and tested for HIV learn their results. This challenge is compounded in high-risk communities that also grapple with a myriad of concerns, including unstable housing, substance abuse, and mental illness.

For HIV positive clients who do not learn their results, health departments must use disease intervention strategies in an attempt to provide