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P R O C E E D I N G S [8:30 a.m.]

MR. JEHN: I am going to start by reading the conflict of interest statement addendum for today. This brief announcement is in addition to the conflict of interest statement read at the beginning of the meeting on March 9th and will be part of the public record for the Blood Products Advisory Committee meeting on March 10th, 2006.

This announcement addresses conflicts of interest for the discussions of Topic III on proposed studies to support the approval of over-the-counter home use of HIV test kits. For Topic IV, the committee will hear an overview and discuss the research programs of the Office of Blood Research and Review. In accordance with 18 U.S. Code Section 208(b)(3), waivers have been granted to Drs. Donna DiMichele, Catherine Manno and Irma Szymanski.

Dr. Allen has been granted a waiver to participate in the discussions of Topic IV, the research programs of the Office of Blood Research. Dr. Allen has recused himself from the discussion of Topic III related to HIV home test kits. Therefore, Donna DiMichele is going to be the acting chair for this topic.

Dr. Louis Katz is serving as the industry rep, acting on behalf of all related industry and is employed by the Mississippi Valley Regional Blood Center. His

employer collects and distributes apheresis platelets. Industry representatives are not special government employees and do not vote.

This conflict of interest statement will be available for review at the registration table. We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda, for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that you may have with the sponsors, products, competitors and firms that could be affected by the discussions.

I turn it over to Dr. DiMichele.

Agenda Item: Proposed Studies to Support the Approval of Over-the-Counter Home-Use HIV Test Kits

DR. DiMICHELE: Good morning, everyone. I guess we have a very, very ambitious agenda today, with one hour for public hearing. I understand we now have 20 participants. So, we are going to ask that we move along fairly quickly since we want everybody to have a voice at today's meeting.

I would like to ask Dr. Elliot Cowan from the FDA

to begin this morning by putting forth the topic for today and that is proposed studies to support the approval of the over-the-counter home use of HIV testing kits.

Elliot.

Agenda Item: Background and Proposed Studies

DR. COWAN: Thank you very much. Good morning.

At the last BPAC meeting I described a multi-step process as the FDA considers HIV test kits for home use. Part 1 was seeking input on what information should be provided to validate a home use HIV test kit. Part 2 is the establishment of criteria by which these tests would be evaluated to establish that they are safe and effective for their intended use and Part 3 will be to determine if a candidate home use HIV test kit or kits meets the statutory requirements, statutory and regulatory requirements, for approval, ultimately determining if the benefits of a given test outweigh the risks.

Today is Part 2. First, I would like to remind you where we left off. On November 3, the last BPAC meeting, FDA sought advice from the BPAC regarding the conditions that were necessary to support the approval of a home use HIV test kit. At that point, we asked the committee to consider what studies would be needed to validate test accuracy, test interpretation and medical follow-up based on the provision of informational material

in place of a trained test operator and counselor.

At that meeting, we heard a proposal by OraSure Technologies for its test. There was a discussion of changes in HIV testing practices and counseling recommendations, a discussion of the role of quality systems for diagnostic tests, a discussion of psychological and social issues associated with HIV testing and over-the-counter home use tests.

I should add at this point that evidence was presented -- actually there was no evidence in the literature at least that there is increased risk of suicide as a result of receiving a reactive HIV test result. There was an overview of the over-the-counter review process at FDA. At that meeting and at previous meetings, there were several recurring themes. There were a number of benefits associated with home use HIV test kids. No. 1, anonymous testing potentially leads to more people knowing their HIV status. Earlier diagnosis translates into earlier intervention. There is the empowerment of consumers in their healthcare decisions. There is a potential impact on behavior and public health.

And there are also a number of risks that have been identified and that is that incorrect test results due to improper performance of the test or incorrect test interpretation would have the potential for significant

risk of harm to patients in public health. There is a possibility of inappropriate use of the test or test result and that, for example, is misinterpretation. What we are really talking about here are limitations of the test and the ability of the user to understand what those limitations are.

There is a potential for adverse outcomes after obtaining a test result without live counseling. Inability to reach individuals for follow-up and to perform partner notification, the possibility of coercive testing and the possibility of testing by minors.

What I would like to do now is summarize some of the comments that came from the BPAC on the issues that were raised. The first was a home use HIV test kit should be no less accurate than tests approved for use under CLIA waiver. As part of this discussion the following points were made: that home use HIV test kits should have high analytical sensitivity and specificity. However, we heard that FDA could be flexible on performance levels in the intended use population. The concept here is that if requirements for performance are set too high, then the availability of a home use HIV test kit would be jeopardized. The committee recognized that a home use HIV test kit could play a very important role in public health.

There was the comment, the clinical trial could

be performed in two phases, observed and unobserved. The clinical trial should look not only at performance of the test, but also at the effectiveness of the instructions for use, that it is critical for users to understand limitations of the test, especially concerning the window period, that linkage to counseling and medical follow-up is critical.

This brings us to today. FDA today is seeking advice of the committee on proposed studies that would be needed to validate a home use HIV test kit with regard to test accuracy, test interpretation, medical follow-up, based on the provision of informational material in place of a trained operator and counselor. You will notice this is pretty much the same slide that I put up for the November 3rd meeting, with the addition that we are now talking about, the proposed studies that have been posted for the public and have certainly been distributed to the committee in advance.

I should note that these proposals are the product of a working group consisting of staff, not only from the Center for Biologics, but also from the Center for Devices and with our colleagues at the Centers for Disease Control and Prevention and are based on what we heard at the last BPAC meeting on this subject.

What I am going to be telling you about today and

which you, I hope, have reviewed in advance, are studies to identify potential users of the test, Phase I studies, Phase II studies, Phase III studies and additional recommendations on informational materials, counseling, testing and referral. I will, of course, define what all of these parts are.

First, studies to identify potential users of the test. I am now getting into what we are proposing, that a manufacturer or a sponsor should submit to us in support of an over-the-counter HIV test, sort of supportive approval of a test. Potential uses of the test should be identified by means of qualitative research. Let me define two things here. No. 1, potential users.

We purposely did not say intended users. We expect that a sponsor will identify who would be most likely to use a test like this.

No. 2, for those of you who don't understand what qualitative research is, qualitative research is research that focuses on how individuals and groups view and understand the world and construct meaning out of their experience. In short, it is concerned with understanding the processes which underlie various behavioral patterns. This is a formal process and we would expect that it would be done.

All this is leading to the idea that clinical

trial study populations should reflect the demographics of those users identified in these studies.

Next, Phase I studies. The objectives are to establish the inherent sensitivity and specificity of the test and the second part of that is to demonstrate that the test is capable of withstanding operational stress. These studies would be performed by individuals trained in the use of the test, looking at the inherent ability of the test to perform and to withstand that stress.

The first part, analytical sensitivity and specificity within the context of Phase I. These will be studies similar to those required for HIV tests for professional use, similar to a test that would come in to us for PMA approval. Expected results are that we would propose that -- we would expect that the performance of these tests for sensitivity and specificity would be comparable to approved professional use tests.

However, if the test that is being submitted to us for over-the-counter use has already been approved by FDA, additional studies would not be necessary because those studies would already have been done to support the initial approval.

Flex studies or operational stress studies, for this a thorough hazard analysis should be conducted and studies should be done to evaluate the ability of the test

to withstand potential sources of error. Also, the device should be designed with a procedural control that is sensitive to all applicable system errors. The type of errors that we are talking about include operator errors, human factors, errors related to specimen integrity and handling, such as excessive specimen application should address such things as reagent integrity and also environmental factors, changing the temperature, changing the lighting conditions, changing humidity, that sort of thing.

Phase II, the objective of Phase II studies is to evaluate in a controlled setting the effectiveness and safety of sample collection by untrained potential users; the ability of untrained potential users to perform the tests properly, the ability of untrained potential users to read and interpret the test results; the performance of the test in the hands of untrained potential users and to evaluate the reactions to test results by untrained potential users.

Again, these are observational studies, the format of which is that untrained users would perform the tests by themselves while being observed by individuals trained in the use of the test. In this case, the actual -- although the individual who would be observed, we would expect that the actual testing setting should be simulated

as closely as possible, physically separating the trained tester from the test subject.

Now the different parts of the Phase II study, to evaluate safety and effectiveness of sample collection. The study participants should be monitored for their ability to properly collect a test specimen and any deviations from the procedure should be noted, along with a possible impact or any impact on the test results.

To evaluate the ability to perform the test properly, the study participants should be monitored for their ability to follow the instructional materials on running the test after the specimen has been collected, again, noting any deviation from the instructional materials.

The ability to read and interpret test results consists of three parts. No. 1 is interpretation of self-testing of their own test results, interpretation of testing of weak reactive and negative specimens and interpretation of examples of text results. So, under the category of the ability to read and interpret test results, there are three different types of studies that we are proposing.

No. 1, of course, is the ability for the individual to interpret his or her own test results and that is to look at the ability to correctly interpret that

test result and to identify any follow-up actions that should be taken consistent with the informational materials which have been provided with the test kit and also to compare the results of testing by those untrained potential users to the results of testing by trained personnel using appropriate statistical methods.

I should note at this point that we are proposing, as you will see in our proposal, that there should be 95 percent agreement between the untrained potential users and the trained users, trained personnel.

Second part, interpretation of testing of weakly reactive and negative specimens. This would be a supervised study in the presence of a trained user considering the fact that the material would be potentially infectious; 120 aliquots of weakly reactive and 120 aliquots of negative specimens would be evaluated by 240 study participants, each person receiving one of these aliquots and determining what the results should be.

The expected performance here, again, is the point estimate of at least 95 percent for the weak reactive specimen and for the negative specimen 99 percent.

The third part, also supervised. Interpretation of examples of test results. The study participants, whose HIV status is not known prior to testing to avoid bias, will be evaluated for their ability to correctly interpret

a set of test results, non-reactive, strongly reactive, weakly reactive and invalid. We envision this as real devices, which would be set up with permanent test results, looking again at the ability of people to correctly identify test results.

Expected performance here as a lower bound of 95 percent confidence interval for percent agreement would be at least 98 percent for the non-reactive, strongly reactive and invalid specimens and 95 percent for the weakly reactive specimens. Evaluation of test performance under Phase II, some comments on the number of people who would be enrolled. The number of untrained users participating in these studies should be sufficient to demonstrate that the lower bound of the two-sided 95 percent confidence interval is at least 95 percent for both sensitivity and specificity.

To put this in the context, our expectations for a rapid HIV test for professional use is 98 percent for both sensitivity and specificity as the lower bound of the 95 percent confidence interval. For these tests we are proposing 95 percent, having heard the BPAC that setting the bar too high might prevent tests from not being approved for over-the-counter home use.

We would expect that at least three geographically diverse clinical trial sites with a high

prevalence HIV infection would be used for these studies. We recognize that large numbers of untrained users will be required to demonstrate the level of sensitivity that we are proposing, 95 percent and considering the prevalence of HIV infection in the U.S., therefore, we are proposing that known HIV positive individuals may be included in this part of the clinical trial. However, we propose also that there be at least ten HIV positive individuals, who would be identified by testing of and by the untrained potential users, who are not aware of their HIV status.

Phase II, reactions to test results. The objective of these studies of this part of the Phase II rather, is to validate the adequacy of the informational materials to inform the study participant about the limitations of the test and about the need to confirm a reactive result, about the availability of resources for counseling and medical follow-up and to have the study participant properly dispose of test-related waste.

This part of the study would also monitor untrained potential users of the test for the reactions following the interpretation of the test results. For example, this could be done through interview or by questionnaire. The sponsor should assess the likelihood of appropriate follow-up by the study participant and use cognitive evaluation to assess on the responses of the

individual and, of course, to note adverse reactions and take appropriate actions as necessary.

Some additional notes on Phase II. Phase II will also include reference testing by trained users. This would not be necessary, of course, for a test, which has already been approved, but for a new test, a prior, previously approved or licensed test should be used as a reference test. For those specimens that give a positive result on any of the testing, either by the individual or by the trained tester, a follow-up specimen should be collected for confirmatory testing.

Informed consent should indicate that study participants my or may not be observed. This takes us now to the Phase III studies, which I am going to break down even further. The objective of Phase III is to evaluate the home use HIV test kit in an unobserved and uncontrolled intended use setting. The key concept in these studies is the need for the test to be performed in a potential use setting that as closely as possible resembles the real world use of the test kit. In other words it is taking it out of the controlled setting into the uncontrolled setting as a way of gradually introducing it into the marketplace.

However, we have multiple options for the conduct of Phase III studies. Yes, there are lots of layers here.

Option 1. The objectives for an Option 1 Phase

III study would be to evaluate the performance of the test, including sensitivity, determination of sensitivity and specificity in the hands of untrained potential users. This would be done by providing a test kit to study participants to perform unsupervised testing at a time and at a place of their choosing.

Evaluating performance in this way would require would require some mechanism to communicate the test result to the study monitor and a mechanism to collect a specimen for reference testing. Reactions of study participants to the test results would be evaluated and there should be a validation of the informational materials to communicate the proper use of the test, communicate test limitations, have the study participants seek follow-up testing and referral to care and effectively provide a route to counseling and also to validate the counseling system.

Performance expectations under Option 1 for Phase III are similar to what we would expect for the Phase II studies and that is that the number of untrained users would be sufficient to demonstrate that the lower bound of the two-sided 95 percent confidence interval is at least 95 percent for both sensitivity and specificity. Use at least three geographically diverse clinical trial sites with a high prevalence of HIV infection.

Let me clarify here that by diverse clinical

trial sites in the case of tests that would be used in the home and at a time and a place of the individual's choosing would be more along the lines of conducting this trial in geographically diverse areas around the U.S.; in other words, not just restricted to San Francisco, to New York, to Boston, but scatter the individuals who are being tested to recognize that there are diverse populations across the U.S.

Again, recognizing that the prevalence of HIV can be relatively low in the U.S. and, therefore, increasing the size of the trial, we would allow the use of known HIV positive individuals to be part of this, but, again, would propose that at least ten people who are infected with HIV but didn't know it previously would be identified in the course of these studies.

That was Option 1 under Phase III. Option 2 to consider -- these are all alternatives we would like you to think about. Option 2 is limited to evaluating the ability of the informational materials to communicate the proper use of the test, the test limitations, have the test subject seek follow-up testing, effectively provide a route to counseling and also to validate the counseling system.

For this option, test kits would be provided to study participants to be performed in an unsupervised setting, again, at a time and at a place of their choosing,

as in Option 1. But in this case, the sensitivity and specificity would be determined from the Phase II studies. The rationale is that the test performance derived from Phase II studies, in other words, sensitivity and specificity is determined under Phase II, the observational studies, would reflect the test performance in the potential use settings. That is the assumption that is being made here.

This takes us to Phase III, which is that Phase III studies aren't necessary. This assumes that Phase II studies would be sufficient to establish test performance in potential use settings and validate the effectiveness of the informational materials. So, in other words, by selecting this option, in other words, not doing Phase III studies, that everything done under Phase II would cover all of our concerns. And no additional information, useful information would be provided by doing those additional Phase III studies.

Some additional recommendations. The labeling should clearly communicate the need to read the informational materials prior to conducting the test. The informational materials should be easy to comprehend by potential users of the test. The informational materials must clearly communicate expected performance of the test kit based on the clinical studies, including the number of

false positive and false negative results that would be expected to be observed by using a test such as this.

The informational materials must clearly communicate the limitations of window period testing. A test manufacturer should be prepared to offer users advice and referral mechanisms to obtain proper medical follow-up of test results. Informational materials must clearly communicate actions to be taken in the event of a reactive test result.

Clear and convenient methods for follow-up testing and referral must be established and communicated in the informational materials. Counseling must be accessible by means appropriate to potential desired users, should be available at any time, in other words, 24/7, and counseling information must be clearly communicated in the informational materials.

This takes us to the questions and I think I am actually under time. The chair is happy.

Let me present to you the questions and then we will move on from here for discussion. Question No. 1, does the committee concur with FDA's proposed criteria for test performance; that is analytical sensitivity and specificity, being equivalent to currently approved rapid HIV tests and clinical sensitivity and specificity, that is, 95 percent for sensitivity and specificity is the lower

bound of the 95 percent confidence interval in contrast to the 98 percent.? Does the committee concur with those criteria for home use HIV test kits?

Question No. 2, does the committee concur with FDA's proposal for the Phase II study?

No. 3, for the Phase III studies, which of the options presented does the committee recommend? Option 1, Option 2 or Option 3, Option 1, of course, being the full study involving determination of sensitivity and specificity, as well as validation of the informational materials.

No. 2, only looking at the informational materials and No. 3, that there would not be a need for Phase III studies at all.

No. 4, this is a question that was similar to what you saw at the last BPAC meeting, does that committee concur with FDA's proposed content for informational materials provided with home use HIV test kits and the steps that should be taken to validate the adequacy of those informational materials to communicate or provide pathways to adequately address issues, including accuracy of testing, correct test interpretation, the importance of supplemental testing for confirmation of positive results, management of psychological and social issues, availability of counseling and medical referral.

The last question, No. 5, if the committee does not concur with any of the proposals in Questions 1 through 4, what additional information or modification would be needed to support approval of a home use HIV test kit?

Thank you very much and we sincerely look forward to all of your feedback and comments.

DR. DiMICHELE: Thank you very much and especially thank you for being ahead of time.

To the committee, we have been given a major charge to accomplish before lunch time here. I think we need to really clearly understand what is being proposed by the FDA. So, I would like to give the committee the opportunity to ask Dr. Cowan some questions at this time.

Are there questions from the committee? Dr. Szymanski.

DR. SZYMANSKI: I would like to ask whether in the Phase II, the individuals are going to be anonymous?

DR. COWAN: I am sorry. I am having a hard time hearing with the speakers the way they are.

DR. SZYMANSKI: Are they testing individuals going to be anonymous in Phase II?

DR. COWAN: In Phase II we had not imposed the need for anonymous testing. It would be up to the sponsor to determine if anonymous testing would be a necessity. If anonymous testing were in place, we would certainly expect

that there would be a way to certainly to obtain follow-up specimens for additional testing if needed, to get the correct test result.

DR. SZYMANSKI: What about Phase III, if it occurs?

DR. COWAN: Phase III could certainly be anonymous, recognizing, of course, that those who would participate would prefer to be anonymous and that is a -- anonymous testing is one of the reasons that people would seek out an over-the-counter test.

DR. SZYMANSKI: Now, then about availability and counseling, why it has to be 24 hours? Would people really try to call at the middle of the night about those results? I mean, nowhere else is there availability at those hours.

DR. COWAN: I am sorry, just to make sure I heard right, the counseling --

DR. SZYMANSKI: The counseling was at 24/7. Why is it necessary to have it at night? That would be quite inconvenient, I would think.

DR. COWAN: Are you asking why is it necessary to have counseling around the clock?

DR. SZYMANSKI: Yes. Just to have it daytime hours everyday, every week day or weekend day.

DR. COWAN: People would use this test at any hour and when they get -- if someone would get a reactive

test result, for example, we would think that they would need to receive counseling at any possible time. So, it would be necessary to make that available when people need it, not just to wait until the next morning, for example.

Am I answering the question correctly or --

DR. SZYMANSKI: Yes, you do, but I am still surprised that they couldn't wait until morning to ask.

DR. BALLOW: As part of the process for either medical advice or counseling, do you envision in that process to have some kind of checks and balances or an audit system to try to ensure that, you know, once a patient or an individual gets the result, obviously, in this case a positive result, that there is some kind of quality process or checks to make sure that they actually seek medical advice or counseling?

DR. COWAN: As part of the studies, are you referring to --

DR. BALLOW: Yes. Was that the intent of say Phase III, for example?

DR. COWAN: We would expect that a sponsor would be able to address all of the issues that we came up with here in whatever way they would like, as long as they are addressed. So, yes, we would expect there to be some follow-up to identify the number of people, for example, that would seek follow-up testing, that would respond as we

would expect them to after getting a test result.

DR. BALLOW: So, you are going to wait to see how companies respond to that point --

DR. COWAN: Exactly. That is actually a good point and it is something that I should raise here and that is when we were developing these proposals, we were walking a fine line. We were on the one hand trying to decide what it is that we absolutely needed to see and on the other hand did not want to restrict companies on their ability to be creative in addressing these issues. So, rather than define very carefully the way that a lot of these studies should be performed, we thought it would be best to outline the general information that we would expect to see and then leave it up to the sponsors to come up with what they think are the appropriate ways to address those issues. At that point it would be incumbent upon us to determine if the solutions that the companies or sponsors came up with would be appropriate to address those -- each of those points.

DR. FINNEGAN: Is there any present literature from the HIV community that people follow up on a regular basis following their present testing? In other words, after their initial counseling, do 80 percent of them follow up or do they all sort of disappear?

DR. COWAN: From what I have seen of Dr.

Branson's talk, I believe he is going to be addressing that. So, if it is okay, I would like to defer to his talk and he will cover that.

DR. KATZ: Any consideration been given to doing the counseling at access to the test kit? Any consideration to requiring a counseling approach when people access the test kit?

DR. COWAN: That is certainly one approach that could be used by a sponsor. We were thinking -- well, again, it is up to the sponsor to come up with a particular approach. Some may feel as though that might be too restrictive because people don't want to have the direct counseling right there. They want to take the test at home and not do it right there, but, sure, that is certainly a possibility.

MS. BAKER: I see the requirements for geographic mix, but also is there any requirement that -- for gender mix in the proposed studies?

DR. COWAN: That would be addressed in our first point, which is that the people who would be enrolled in the clinical trial would be expected to represent the potential users of the test and if that represents both men and women, which I would almost certainly think that it would, then we would expect to see -- we would expect to see an equal mix of men and women, I would think.

DR. DiMICHELE: I actually have a question. I actually have two questions.

Do you anticipate in terms of how these studies would be designed and the results that you are anticipating, can there be overlap between the Phase II participants and the Phase III participants or do the Phase III participants in the study, untrained users, have to be a different population than the Phase II untrained users?

DR. COWAN: It is a possibility. I guess my only concern with overlapping the Phase II and Phase III participants is that ideally you would like to have people who haven't taken the test before and see how they would react. If they have already had a sense of how to use it, Phase III is a bit biased.

DR. DiMICHELE: That is what I would have thought.

Could you remind me to what grade level informational materials are supposed to be targeted?

DR. COWAN: Again, that would be covered by the qualitative research that will be done up front.

DR. DiMICHELE: So, there are no general guidelines about how that is done?

DR. COWAN: We have no general guidelines right now. For CLIA waive tests, I believe the reading material should be set at a seventh grade level. That doesn't

necessarily apply here. When I say that, my guess is it will be lower because I know there was considerable discussion at the last BPAC meeting about people who either had a much lower reading level or were illiterate. The identifying potential users should make some inroads into identifying the best level to set those informational materials.

DR. QUINN: Elliot, just remind me from our last discussions on this, although we are looking at it from a federal perspective being the FDA is a federal agency, HIV testing is regulated by states. I mean in terms they have their own regulations in terms of pretest counseling, post-test counseling, et cetera. How will this be -- you know, if this was ever 1 through the Phase I, II, IIIs and came out with glowing results, it then has to go through state regulatory submissions as well independently to get licensure within that state. Is that how it would work? Just clarification.

DR. COWAN: Yes, it is something that I am not as familiar with. Dr. Branson can -- I think will be able to address that if we can just defer that over to Bernie, I think that would be better.

MR. SHARP: I just have a question about the referral process and I don't know whether this is the right time to ask about this, but, you know, the CDC has put

forth a lot of recommendations for testing recently and community-based organizations are doing a lot of the testing and counseling now. So, I think it would be optimal to have a really good list of referrals including community-based organizations in those referral lists, depending on I guess where the site is and where the counseling is being done.

DR. DiMICHELE: We will take this as the last question.

DR. QUIROLO: I just have a question about -- so, the sponsor is going to determine who the populations are going to be to be tested and the FDA is not going to determine whether there should be socioeconomic and racial or any other expectations of the manufacturer. So, you don't -- you are not defining the minimum for the socioeconomic and racial --

DR. COWAN: We are not defining that a priori. We will be relying on the studies that are being done initially, the very first part of this, which is to identify the potential users and then evaluate if those studies, number one, have been done correctly and, number two, if we agree with the conclusions based on the information that the sponsor is providing, as well as certainly looking at the literature and getting advice from our colleagues at CDC as well. We will be putting the

burden on the sponsor to tell us who they think will be the potential users of the test and then gear the test accordingly.

DR. DiMICHELE: Okay. Last comment, Mr. Sharp.

MR. SHARP: Just quickly, I had hoped that we would also -- you mentioned that we are sure to include gender in the criteria, but also I would like to recommend age and getting youth into the trial as well.

DR. COWAN: Thank you.

DR. DiMICHELE: Okay. Thank you, Dr. Cowan. Really appreciate it.

To stay on time now, we are going to move on to Dr. Branson's presentation, the clinical experience with approved rapid HIV tests. Dr. Branson is from the CDC.

Agenda Item: Clinical Experience with Approved Rapid HIV Tests

DR. BRANSON: While he is setting up my slides, I would like to start by responding to Dr. Quinn's question. At least in the precedent with the home sample collection kits, under the Interstate Commerce Regulations, federal approval preempts state restrictions. So, in that particular case when there were certain state requirements and certain states would prefer to not have had the test introduced, the Interstate Commerce Regulations say that the federal approval because this is an over-the-counter

thing preempts more restrictive state laws. So, I do not think that it is likely -- that was the opinion at that time of the Office of General Counsel and I suspect it would be the same for a home use test kit that the federal approval would then take precedence over whatever the states did at that point in time.

I am going to speak a little bit about clinical experience with approved rapid HIV tests and in particular I would like to start out with some background after the last committee discussion on preliminary results, positive predictive value discussions that have been had in that regard in the past, also talk about counseling messages when you have a preliminary positive test result and then our experience somewhat with postmarketing surveillance of rapid HIV tests, the experience with rapid tests in urban programs and then our recent investigation of false positive oral fluid test results.

In 1989, with the introduction of the interpretive criteria for the Western blot, the public health service recommended that no positive test result be given to clients or patients until the screening test was reactive and supplemental, more specific tests, such as the Western blot had been done. At that time, this is because of concern for giving false positive results to individuals. So, the blanket general recommendation was

that preliminary results would not be given and, in fact, this pretty much precluded the availability of rapid HIV tests in the United States whereby you would have to give a preliminary result.

Studies that were done in the mid-nineties and this is the first of them about on-site rapid HIV testing, provided us some data and information on what happens when you give people preliminary test results. This study did several comparisons, but in particular in this before/after study, they compared conventional testing protocol with the rapid testing protocol in an STD clinic at that time using the SUDS test.

As you can see in the conventional testing protocol, only about 30 percent of individuals return for their test results. While a higher proportion of individuals who are HIV positive received the results, most of that was the result of active outreach in order to identify those people and provide them their test results. Whereas, giving people preliminary rapid HIV test results as you can see here, 97 percent of people receive their results in the vast majority after receiving a preliminary positive result, came back on their own for the test results and did not require outreach efforts in order to provide their test results to them.

So, this difference was a substantial one and it

was one that, you know, answered, I think, some of the concerns because this is one of the few studies, which actually measured the difference in effort necessary to give people their test results under one strategy and the other. We used those data back in the mid-1990s on the basis of HIV test results and the prevalence that each one of the different kinds of HIV testing sites noted to construct a quantitative decision model to say basically what would happen to the receipts of test results if rapid tests were used in publicly funded testing sites. So, the return rates we compared with those that were determined in the study for HIV positive and HIV negative people and were done and then we compared for all the testing sites in the U.S. based on the CDC's client record counseling and testing database. At this point that data were from 1995 in order to calculate what the differences would be.

This was published in 1998 when we came out with the new recommendation and I think that the key ingredient here was that under the rapid test algorithm basically, 8,000 more individuals would end up limiting their test results and had done so with conventional testing. The cost of that would be that approximately the same number, 8,000 people would receive an initial false positive screening test. Now, the analysis, the decision analysis, was done based on the SUDS test, which coincidentally had a

specificity of 99.6 percent, which is the same as the lower bound of the confidence interval for specificity of the OraQuick test with oral fluid. So, this might be considered somewhat similar to what we would see. Now, I think that is a real difference that we are talking about here is that there are definitely anticipated false positives that we would see, but the advantage that was perceived is a larger number of people who were truly positive would learn their test results with Abbott HIV tests.

So, in 1998, the Public Health Service changed its recommendations to encourage providing preliminary positive HIV test results before the confirmatory results are available in situations where tested persons benefit. This in particular related to those environments, especially like STD clinics and other places of episodic care, where people were tested for HIV and did not return for the results, whether positive or negative.

Now we talked a lot last time about negative predictive value of a single test and obviously, it depends on specificity of that test and these are for some of the currently approved HIV tests, all of which have high specificity, but depending on prevalence as you see in these columns, there is a considerable difference in the positive predictive value for the test.

This is important at a population level and perhaps somewhat less so at a patient level and, obviously, the converse is negative is negative is negative predicted value also depends on sensitive of the test and varies with the prevalence, but given our current tests, basically, where you have to really reach a very high prevalence level before you see a difference in the negative predictive value of a test to more than four significant digits.

So, this is the reason why negative tests do not require confirmation and positive tests do. Now, when we had begun introducing rapid HIV tests, there was some research done on something called qualitative interpretation of quantitative probablistic expressions, which is just about as confusing as the title sounds. The issue is is that, you know, when someone is trying to tell the difference between 90 percent predictive value and 85 percent and 60 percent predictive value, those numbers don't really make any sense and so we tested terms like very likely you are infected, somewhat likely you are infected, it is possible that you are infected, there is a chance that you are infected.

After having a couple of year's experience with this, we decided to completely abandon the topic and CDC's current recommended counseling message for individuals with a reactive screening test, a rapid test, is basically if

you say your preliminary result is positive and we don't know for sure if you are infected until we get the results from the confirmatory test.

So that we do not attempt to even in a counseling situation where you do a risk assessment estimate how likely it is that the person may or may not be false positive depending on prevalence, but quite simple state we need to do confirmatory testing and in the meantime you need to take precautions to avoid transmitting the virus until we have an answer with some degree of certainty from supplemental testing.

In terms of the background of the surveillance I am going to talk about, the OraQuick test, in particular, which is the first one approved by the FDA as a CLIA-waived test, it was approved in November 2002 and waived in February 2003, later approved for oral fluid in March 2004 at which time the name of the test was changed. We initiated our postmarketing surveillance in 2003 when the test first started coming into more common general usage.

I presented some of these data at the last meeting, but overall the median seropositivity and specificity for the project areas that were participating in our postmarketing surveillance, this involved 17 project areas with 368 testing sites. For whole blood specimens among 135,000 people, the specificity was 99.98 percent and

for oral fluid testing, among 26,000 people, the observer specificity, the median was 99.89 percent. So it was slightly lower with oral fluid from this test, but still well within the range of FDA's expectations for both specimen types.

Now, part of the issue with predictive value, I think, that leads to a lot of confusion is that the difference in predictive value does not have much to do with the number of false positives. As you can see here, the number of false positives is the same for whole blood and for oral fluid but the predictive value for one is 97 percent and for the other is 50 percent. So, the difference in predictive value has got to do with the number of true positives and not with the number of false positives. I think there is a lot of confusion that in low prevalence settings, there is a perception that the number of false positives increases in a low prevalence setting.

The issue is that the number of false positives is a product of the specificity and it is the same no matter what the prevalence is. However, if the number of true positives goes down, which is a function of prevalence, then you see this large effect on predictive value. So that in all these settings where we have about the same number of false positives, you can see vastly different numbers in positive predictive value on that and

that is mostly a function of how many true positives are in that environment. I think this is a very widespread confusion on people's part, thinking that in low prevalence settings, we are going to see a bigger problem with tests where in fact the difference is that we just detect fewer true positives in those kinds of settings.

Again, these are data from our postmarketing surveillance in different environments. Now, our other data on rapid test implementation comes from some of the major urban areas that have been tracking their usage. So this is from Chicago during the calendar year 2005, where they evaluated the test with 14 community-based partners and in seven public health clinics around the city of Chicago. Basically, in the community-based testing in outreach settings out of about 4,800 tests, there were 78 1.6 percent confirmed positives and in the clinic setting, out of 3,200 tests, there was again about 1.6 percent of individuals , who confirmed positive.

The big difference is that in receipt of test results in 2004 before the introduction of rapid HIV testing, about 65 percent of people received their HIV test results and in 2005 after the introduction of rapid testing, 94 percent of people received their HIV test results. In Chicago's experience, there were only seven false positives among 12,000 people tested before 2004 and

2005, with rapid HIV tests and at the current time, Chicago has introduced rapid HIV testing in all of their HIV and STD clinics.

In San Francisco, as of the third quarter in 2005, 46 percent of all their HIV tests are conducted using oral or finger stick rapid HIV tests and as you see here, you know, based on their numbers, out of about 5,700 oral rapid tests represented 35 percent of all their testing, a positivity rate here of 2.4 percent. The finger stick represented about 11 percent of their testing, 2.3 percent and in many jurisdictions we would see the same phenomenon that oral fluid testing ends up being very popular and takes on an increasing proportion of the testing.

This bottom line figure for conventional testing, as you see, has a higher positivity rate and as this program and others explained many individuals coming back in for repeat testing with conventional tests, once they have been positive in order to document or validate their positive status and so sometimes you will see an inflation of the positivity rate for conventional testing as a result of repeat tests as opposed to initial screening tests.

In Los Angeles, they gather the data somewhat differently and they basically have nearly 50 percent of their tests as well, where rapid HIV tests compared to their conventional tests In this group of 9,900 tests,

they experience nine invalid test results. They had data on 137 preliminary positives because they introduced a new data collection system at the same time they introduced the rapid tests. They are having some trouble with the follow-up data and so there another 51 individuals with preliminary positive rapid tests for which data were not entered into their system, but of these 137, 131 confirmed to be true positives, three were false positive. Two gave inconclusive results in one of those individuals has a result at the time of this data collection were pending.

So, still a good experience with reasonably good specificity of the test. Houston collects the data again, somewhat differently and their testing currently is split about 50/50 between rapid testing and conventional testing. Among the individuals who were rapid test, this refers to post test counseling percentage, which means how many people got their results. During this time period, most of the calendar year 2005 of rapid tests, nearly 99 percent of people received their test results where less than 50 percent of people received of people receive their conventional test results.

In terms of new positives identified, the prevalence was higher again among the individuals who were tested conventionally, but as you can see, only 43 percent of people who tested positive with conventional test

results received their test results in Houston, where a hundred percent of the individuals tested with rapid tests received -- and these refer to confirmed test results, not preliminary tests results in those situations.

So, what we had anticipated with changing the recommendation in 1998 does appear to have occurred, that people do come in and receive their test results and receiving a preliminary positive result, encourages people to come in for confirmatory test results. This difference, a receipt of test results is what we feel is a very important advantage of people getting rapid testing because even if you have a very accurate test if only 43 percent of people receive the result, it basically means the test has 67 percent specificity effectively.

Now we did an investigation of false positive oral fluid rapid test because in December of 2005, there were media reports in the San Francisco Chronicle, The New York Times and The Los Angeles Times about difficulties with an excess number of false positive HIV tests. Now, we for our sources of data use four prospective studies that CDC had conducted in which parallel testing of whole blood and oral fluid with the OraQuick test was conducted at the same time as an EIA and when indicated a Western blot. These studies were conducted between 2000 and 2005. Because many of these false positive results happened in

the fall of 2005, we conducted an outlier analysis, looking at 41 specific testing sites in three different states, including the two states, New York and California, where the false positives were reported and I will also present to you some recent testing data from the New York City STD clinics between December and January of this year.

Now, from our four prospective studies, I presented these data at the last BPAC meeting. The specificity with whole blood was 99.9 percent, testing 12,000 with oral fluid and 99.6 percent overall, very similar to the specificity of the serum EIA, 99.7 percent. Breaking those studies down, however, in Los Angeles, where we had conducted about 5,300 tests, there were 21 false positive oral fluid tests compared to four with whole blood, compared to 23 with the standard EIA for an overall specificity of 99.6 percent.

In the MIRIAD study, which tested pregnant women at the time of labor and delivery, a substudy was conducted where both whole blood and oral fluid testing was performed in approximately 2,300 women in six cities in the United States in 16 different hospitals. The overall specificity with oral fluid was 99.6 percent and as you can see from both of these categories essentially that the specificity of oral fluid and of the EIA were essentially equivalent. In fact, there was slightly more false positives with the

EIA than there with oral fluid.

Now, on the other hand, there were two studies in these four, one was conducted in Phoenix in an STD clinic and HIV testing site in which there were five false positive oral fluids, no false positive EIAs and three with blood. Again, specificity of all those tests was quite high. However, in an outreach study in Minnesota in about 2,400 tests, there was a significantly larger number of false positives with oral fluid, as you see here, for an overall specificity of only 99 percent of the test and considerably different than it was with the EIA.

So, we conducted a subsequent investigation when these false positives were noted. First of all, in that study over a two year period from March 2002 to March 2004, there had only been seven false positive tests out of 2,017 people who were tested. Then between April 2004 and August, there were 16 false positives out of 407 tests. So, there was a sudden cluster of false positive tests for a lower specificity.

During that time period, the technicians reported that these tests appeared qualitatively different from the usual positive tests and that they were very faint. We initiated a follow-up study in order to identify the cause for this and so we set up to do a case control study in nine sites and three states between February and May 2005.

There were 2,314 tests conducted and not a single false positive occurred in that group. So, the case control study could not proceed because there were no cases.

In terms of looking at our outlier analysis in the more recent time period, this is a statistical process control chart that we use. The green bar here represents the proportion, 0.4 percent of what we expected or allowable numbers of false positives. The Y axis here ranges from 0 to 1 percent basically so that we are talking about, you know, relatively small numbers overall. At each of the testing sites, we on the basis of the number of tests they conducted calculated 95 percent confidence intervals, which are represented by these red bars for the proportion of tests that could be false positive and still meet the performance expectation.

In other words in a site like this, where they only did 20 tests, you might get one false positive and your rate of false positives would be 5 percent. But because of the small sample size, it would still, you know, meet the 95 percent confidence interval.

And a result of doing these analyses in New York City, New Jersey and San Francisco, we identified those sites where the proportion of false positive fell outside the 95 percent confidence interval that we would expect. There was one site in San Francisco and three sites in New

York City that were not within the expected range of false positives. In New York City, the three sites with excess false positives, as you see here, the specificity range from 98 percent to 99.8 percent in approximately 1,500 to 1,700, simultaneously in the same city with the same lots of test kits at the other seven testing sites, they basically did not experience any increase in the false positives.

So, we are investigating what is going on in those specific clinics and there is a similar situation in San Francisco in that there was one site with excess false positives which rather consistently reported a low specificity and the other 11 testing sites in the city with the same tests and the same kind of training, did not experience difficulty with the specificity.

So that our conclusion from that was that there are potentially some site or technician specific factors as opposed to test specific factors related to these false positives.

In New York, they are doing a considerable amount of testing, three to four thousand rapid HIV tests per month. And New York experienced with the introduction of oral fluid tests a 30 percent increase in their testing volume at STD clinics. So, when they started to see the specificity go down, when you take this as the overall

total for all their clinics, including the three clinics that experience more false positives, they suspended oral fluid testing in December and went over to finger stick testing only and then they resumed testing in December with oral fluid tests and I will show you the algorithm that they are currently using, but with the resumption of oral fluid testing, they did see some resolution of the specificity problem.

Now, what has happened in both San Francisco and New York City is they have adopted an interim algorithm whereby if a person has a reactive oral fluid test, they then perform a finger stick test because all of our data shows that the sensitivity and specificity of testing with whole blood is better than it is with finger stick. If an individual has a positive oral fluid test and a negative finger stick test, they are given a counseling message that the oral fluid test was reactive but that usually the whole blood test is a more accurate test and they still get confirmatory testing, but the message says it is likely that you are not infected. If there are concordant results of the oral fluid test and the finger stick test, both being reactive, the client is told that both tests are reactive, that it is most likely that they are infected and, again, they go on to do confirmatory testing.

At least in the first month's data that we have

of that algorithm in New York City, there were 69 reactive oral fluid tests. The follow-up finger stick was reactive in 32 individuals and I have gotten this result here, all 32 of those individuals who had reactive oral fluid, reactive finger stick, were also Western blot reactive. There were six individuals who refused the finger stick, all of who were positive and of those who had a reactive oral fluid test and a negative finger stick , all 31 individuals proved to be negative. These two at the time I made this slide were indeterminate and in both of those cases, we have a month later follow-up specimen, where the people proved to be HIV negative.

So, at least in this circumstance following a positive oral fluid with a finger stick was able to resolve the difficulty with false positive tests. So that overall, our conclusions are that rapid HIV tests demonstrate high specificity, but as with all screening tests, the false positives will occur and they should be expected. This is something that when we changed the Public Health Service in 1998, it was concluded after a general consultation that the benefit of more people receiving the test results outweighed the disadvantage of some false positive tests, but obviously confirmatory testing after a reactive test must always be performed.

Clearly, more persons learn their HIV status when

they receive timely results from rapid tests than with conventional testing when they receive no results and they have to come back for test results in two weeks.

With respect to OraQuick, its specificity is slightly lower with oral fluid than with whole blood, but well above the FDA's minimum threshold, the lower bounds, the 95 percent confidence interval being 98 percent with both oral fluid and with whole blood specimen types. These excess false positive tests in oral fluid occurred in a limited number of sites. They appeared to be related to unidentified so far sites or host specific factors and we hope to be able to conduct a case control study in order to better identify what some of the co-factors may be related to these false positive test results.

I would just like to acknowledge the individuals who provided data and information for this presentation.

Thanks.

DR. DiMICHELE: Thank you very much, Dr. Branson. A lot of information in a very timely way.

We are getting close to needing to start the public hearing. But I was wondering if the committee had any questions for Dr. Branson. We have time for a few questions.

Dr. Quinn.

DR. QUINN: Bernie, just in terms of the follow-

up, they give just definition -- because you see 98 percent follow-up, is that when you use that term, does that mean that they are getting follow-up counseling after the rapid test or does it include after confirmation of the initial screening test that they actually came back to a clinic and got their Western blot results?

DR. BRANSON: The situation is that is a very, very difficult figure to determine. What our experience has been in several places is that when a person goes to a testing site where all they do is testing and they receive a preliminary positive test result, very often those individuals go to a care site instead of coming back to the testing site. When we do follow-up up them, by the time we find those individuals, they have already had a viral load and a CD-4 count done. So that instead of coming back and getting a Western blot and then getting referred to a care site, very often they will do that. In some of our more successful studies, for example, in emergency departments, it is designed specifically that a person would go to a care site to receive their Western blot test result in order to take out one of the steps in follow-up that might result in some attrition.

DR. DOPPELT: Just a quick point of clarification. When you said on the oral test that there were, you know, these false positives that then half of

them turned out to be not so, were those weakly positive?

DR. BRANSON: What we do see are occasions where there is a concordant false positive, where both oral fluid and whole blood is false positive and those tend to not to be weakly reactive, but when we have this discordance between the oral fluid and the whole blood, most of those are described as faintly false positive. In attempting to quantify them, they appear to be less intense than the low level positive control that is used for the test. So, there has been some subsequent investigation to see what might be going on with co-factors and it appears at least from some preliminary studies that over-collection, that excess saturation with saliva on the device itself leads to some of these faint false positive results. But these excess false positives all appear to be very faint.

DR. EPSTEIN: Thank you, Bernie, for that very illuminating presentation.

Just one question about the multi-test algorithm. When we approved rapid test we had a lot of discussion about the need for what we called statistical validation to the use of a second rapid test. It would seem that both in New York and in San Francisco, they have gotten around to that. I am just wondering what CDC's current thinking is on that subject.

While you are thinking of your answer to that, a

second question is in the home use setting, should such a test be approved? You won't have that opportunity and I just wonder how you foresee managing the issue of false positives in that setting, which will inevitably occur.

DR. BRANSON: There are two issues. I mean, obviously, CDC is looking into the use of combinations of different tests and we originally conceptualized this, of course, we were thinking basically of combinations used on the same specimen type. We were thinking in terms of blood testing and so we are evaluating all the currently approved rapid HIV tests on the same specimens in order to see whether you can come up with a statistical validation or essentially a confirmation just based on the use of rapid tests. We are nearly finished with that analysis. This change of specimen matrix from oral fluid to a blood matrix is something we had not originally thought about and we are very carefully evaluating this experience in San Francisco and New York, where they are following use of one test on the oral fluid matrix and the same test on a blood matrix and so far that appears to be in effect a statistical validation. We would like to have, you know, somewhat larger numbers before CDC issues a recommendation.

I am sorry. I forgot your second question.

DR. EPSTEIN: Just any comments that you might have about the issue of false positive tests that would

occur in the setting of home use because they are inevitable and, you know, depending on what population self tests if it is dominated by the worried well, well, then the positive predictive value will be predictably low.

DR. BRANSON: I think that is the reason I presented the initial data from the discussions in the mid-1990s. We anticipate that false positive tests are going to occur whether it is home use or in clinic related use. We think that the importance of the instructional material is to make people aware that false positive tests will occur and that they need to take follow-up action. I mean, I don't think we anticipate trying to design the release of several tests and advising people how to do a cookbook algorithm to do their own confirmation at home.

Clearly, this is a screening test. People need to understand that as a screening test, it is designed for sensitivity and those false positives will occur and I think this is addressed by the guidance that Elliot proposed in terms of the instructional materials to make sure that people know that.

I don't think that CDC has any attention of suggesting to people how to sort out whether the test is true positive or false positive at home by using a combination of different tests.

DR. CRYER: That actually answered my question

but I will make the observation that in the L.A. Times article one thing that you didn't mention is how upset the people who had the false positive were I mean, they were -- it was pretty clear to me you would think well I am glad I didn't have it would be the reaction but it was really more -- it seemed like a lot of the people had the reaction of, you know, you just put me through a lot of bad things by having the false positive test. So, I do think that this thing is important. It is pretty clear to me from the article that whatever instructions were given did not let the patient know or the person know in a real way that this could be a false positive test.

DR. BRANSON: You mean, as I studiously avoid presenting any of the data from Los Angeles, in the article that you are referring to, I think that public health by press release is very difficult and in that particular situation in Los Angeles when we investigated it, we found that the technician had not sent confirmatory tests on over half of the individuals. So we had no idea were actually false positive or not in that situation. So that there was a different problem going on in Los Angeles than false positive rapid HIV tests.

DR. BROWN: One of your slides showed a progressively increasing false positives from July through November. Are there any reasons to think that there would

be in a large group or perhaps genetically different individuals who would have a seasonal variation, such that you would expect to find some differences at different seasons because there are certainly a lot of things that change seasonally, biochemically.

DR. BRANSON: Yes, I think we can speculate on that. You know, in the original outbreak or cluster that we saw in Minnesota, it ended up happening early spring and into the summer and we were trying to figure out, well, you know, snow is melting. Are people eating fish or you know what is the difference for what is going on.

The only way we are going to resolve the answer to your question is going to be with a case control study. The problem is that these cases are so rare that it is going to take us sometime to look at the other potential co-factors and sort of speculating about whether it is a seasonal influence or any other kind of influence, I think, is premature right now.

DR. KUEHNERT: I just wondered what the availability in clinics and public health laboratories are of the rapid blood test and I am asking just because of this algorithm and the possibility of, you know, a test being done at home and there being counseling saying if you come in today we will have a test result today that will likely tell you what your status is it is sort of having a

same day result. Is there any thought about how that might work or whether that could work?

DR. BRANSON: This is something that Jay referred to a minute ago, with respect to the multi-test algorithms and I can tell you what current thinking is at CDC right now with respect to that and we really pretty much are looking at essentially recommendations that differ for health care settings versus non-clinical settings versus other kinds of places. In other words when you say about coming in, get a same day result there and then, I think that we would feel comfortable about that happening in the health care setting where people are used to making a diagnosis.

I think that we would probably be less comfortable in a completely non-clinical setting with a person who has had five days of training, following through an algorithm and giving the person a serious diagnosis, like you are conformed to be positive with HIV. So I think our intention is going to be to encourage people to go to health care settings and some of them may be able to do same day point of care combination testing algorithm to give that confirmatory result for people, but I think more important is our making sure to educate people that a screening test is a screening test and just as, you know, positive mammography or PAP smear, you need to take

additional steps in order to resolve the truth.

DR. KUEHNERT: I was just making that point because it looked like your data was very -- the data was very compelling about patients coming back if they thought they would get a test result. So, if they thought that it was going to happen that day and they wouldn't have to wait a couple of weeks, we might see that same tendency.

DR. BALLOW: On the STD sites, San Francisco and New York, where you showed a higher false positive at one of the sites compared to the other, was that blood or oral?

DR. BRANSON: Oral fluid. Right. It was a community testing site in San Francisco and three STD clinics in New York, where it was oral fluid that had a higher than expected --

DR. KATZ: This is kind of a follow-up to Matt's question and your very, very high rates of follow-up. That included all the way to confirmation and some subset of that, did it not? I think once people get the positive screening test, they get into a system in general was the point you were making, but maybe it is unclear how much follow-up those people were getting.

DR. BRANSON: You know, one of the things that we are grappling with is exactly how to measure that because similar to when a person gets a diagnosis of cancer, they can elect whether or not to get chemotherapy. With HIV

testing you get a positive test result and I don't think that we can make it incumbent that says absolutely everybody has to get into care. They have a choice to make at the time they receive their test result. We are attempting to follow both how many people receive their test results and how many people enter care and how many people stay in care. Obviously, there are certain losses at each one of those stages. A lot of that has to do with a person's choice about what they do when they follow up on this and I am not that we can insist that they do what we think is best for them.

DR. QUINN: Very quickly, since you know this field better than anyone I know, WHO does have what was brought up earlier about doing two rapid tests, a screening and a confirmatory. Do they include in that the oral test as well as -- that that could be used as either a screening or a confirmatory test?

DR. BRANSON: At the current time, the WHO recommendations only include that the test should include different antigens or should be based on a different principle. In other words, flow through versus agglutination versus lateral flow. They have not addressed specimen matrix because there has not been widespread implementation of oral fluid tests, except for the OraQuick test.

DR. DiMICHELE: Just to let the committee know, I mean, we will have in our deliberations the opportunity to ask the two speakers more questions should we need to. So I think we really should move on to the public hearing.

Thank you, Dr. Branson. Appreciate it.

Before we begin the public hearing, I am obligated to make an announcement, but before I even make that announcement, I would just like to say once again two things. We do have 20 speakers in this public hearing session. What we would like to do is to actually forego an official break period so that the committee members please feel free to get up and down as you need to during this period. We will take the public hearing session all the way 11 o'clock when the committee will then begin its deliberations. But I do ask that each speaker please be brief to allow all of your fellow speakers the time to make your central points.

What I will do is announce the speaker, as well as the person to follow that speaker so that the follow-up speaker can be ready to come up to the podium as needed.

Before we begin, I would like to make this open public hearing announcement for particular matters meeting, both the Food and Drug Administration and the public believe in the transparent process for information gathering and decision-making. To ensure such transparency

at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. However, if you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

With that, I would like to invite the first public speaker to the podium, Mr. Elliott Millenson, please. This will be followed by Mr. Steven Jackson.

Agenda Item: Open Public Hearing

MR. MILLENSON: Good morning. I am Elliott Millenson and I am here today to present the true history of home AIDS testing, which differs substantially from the fairy tale history presented to this committee at its last

meeting by FDA.

It is important to correct the record, to provide perspective as it has great bearing on your deliberations. In 1985, I founded the company that developed the world's first home AIDS test, although I no longer have any financial interest in AIDS testing.

FDA has blocked home AIDS testing for two decades despite strong scientific support and a compelling public need. Forsaking its role as the watchdog of America's health, FDA became the lapdog of special interests. Yielding to political pressure, FDA ignore unambiguous science and banned home AIDS testing, sentencing tens of thousands of Americans to death.

When AIDS first appeared in the U.S. in the early 1980s, many of those infected with HIV organized and demanded treatments. These AIDS activists demonstrated and lobbied aggressively at all levels of government with particular focus on influencing FDA. Once an HIV test was developed in 1985, making tests as widely available as possible would have been the obvious and logical public health response to a fatal, sexually transmitted disease. But AIDS activists opposed testing, fearful of its impact on their lives. They were afraid that employers, government and sex partners would want to know their HIV sero status. So, public health officials let the fears of

the infected prevail over the rights of the uninfected.

Promoting condoms, despite their high failure rate, became the cornerstone of our national don't ask, don't tell approach to AIDS prevention. The idea, first promulgated by those infected with HIV, is that your partner doesn't need to know whether you are infected. You just have to use condoms. Condoms help.

But the truth is having sex with an HIV infected partner is never safe, even with a condom. A sound public health policy would strongly advocate testing as well as condoms. It would make HIV tests widely accessible and would encourage knowing your partner's HIV status. But public health officials, who knew widespread access to testing could help prevent the spread of AIDS, rejected the clarity of science for the fog of politics.

I conceived the idea for a rapid home AIDS test in 1985, over 20 years ago. By 1986, my company's scientists had determined it was technically feasible to develop a safe, effective and affordable test. So, I met with FDA. I revealed my company's research showing the majority of Americans wanted a home HIV test and that many people would only get tested using a home test, findings later confirmed by CDC.

I explained government could even give away a home test to those who could not afford one, an approach

that would be more effective and economical than a brick and mortar approach of funding hundreds of independent test clinics. FDA told me they would "probably never" -- and I have my notes from that meeting -- probably never consider a rapid home AIDS test.

After meeting with FDA, rather than developing a rapid AIDS test, we developed a vastly inferior product, a blood collection kit. We felt there was a greater chance of overcoming FDA's opposition to home AIDS testing with this as an initial step. In 1987, after successful clinical trials at a number of centers, including Johns Hopkins, we submitted to FDA our premarket approval application, which demonstrated our test's safety and efficacy.

But a perfect political storm hit home AIDS testing. AIDS activists and those with a financial interest in HIV testing swiftly made their opposition known to FDA. Testing clinics, whose funding was linked to the number of tests performed, aggressively lobbied FDA and Congress to block approval of the test.

In March 1988, succumbing to this political pressure, FDA published criteria banning all home HIV tests,, our blood collection kit, as well as rapid tests. FDA concocted reasons for its ban, foremost among them was the claim of a significant risk of suicide with a home

AIDS test. Despite data showing a third of Americans preferred a home test, FDA denied them this choice, claiming it was necessary to compel them to have face-to-face counseling to protect them from committing suicide.

Let me be emphatically clear. There was never any data to support FDA's absurd claim. In fact, there was substantial data submitted to FDA by my company, as well as by experts in the field of suicide prevention that suicide was not a risk.

FDA also invented a plethora of other baseless arguments against home testing. People would engage in risky sexual behaviors without face to face counseling, that during the window period, people would spread the disease if they received a negative result from a home test, but not if they received a test result in a clinic. There were no data to support these claims.

But FDA was not interested in data. FDA was only interested in appeasing special interests. In announcing its ban in 1988, FDA obfuscated, making the seemingly reasonable announcement that they had established five criteria for reviewing a home HIV test application. FDA indicated they would only review applications that met all of their five criteria.

Here are the five criteria. We can stop at the first requirement because it is a show stopper. The

criteria say that FDA will not even review an application for any HIV test unless a professional health care provider administers it in a medical facility. Gosh, your home test is for use in the home by a lay person? I am sorry. We can't review it.

FDA's criteria represented a de facto ban on home AIDS testing. So, FDA refused to even review my company's application, although it contained data responding to the very concerns FDA had raised, this in the midst of a devastating epidemic.

I persevered and continued to fight, often a lone voice. AIDS activists fought back. Armed with no data to support their claims of the dangers of home AIDS testing, they continued to vehemently lobby against such tests. They testified against home AIDS tests at congressional and FDA hearings. They lobbied in numerous states as well, including New York, Florida, Texas and California, where they successfully pushed for legislation banning home HIV tests.

In 1990, three years after our submission, I sued FDA, seeking to compel them to review our data. To settle that lawsuit, FDA finally agreed to review my application and hold an advisory committee meeting. In its story on the settlement, The New York Times reported that "FDA's CBER Director Paul Parkman said the agency was not

softening its opposition to home testing kits that would check blood samples and give a result instantly, tests that are theoretically possible although none has been formally proposed." Theoretically possible, FDA stated in 1990.

The usual suspects showed up at FDA's 1990 advisors meeting to express their strong opposition to our home AIDS test. The laboratory and medical associations. The clinics. The activists. FDA and CDC also expressed grave concerns about the risk of suicides and other completely unsupported issues with no scientific basis. Only one of FDA's advisors had the courage to vote for approval.

Disturbed by FDA's attempt to bias its own advisory committee, this advisor commented, "It was almost as if this matter was brought before FDA's subcommittee on nonapprovability."

After FDA's 1990 advisors meeting, I sued FDA again, seeking an unbiased review. In settlement of that lawsuit three years later in 1993, FDA agreed to again review my application, this time "as expeditiously as possible." The FDA Commissioner's Office indicated, though, that I would need to build political support for our test and reverse state laws before it could be approved. Bernie mentioned federal preemption. FDA's position at that time was that federal preemption would not

apply and that I would have to reverse state laws.

Until then, FDA said, their five criteria from 1988 would still officially be in place. So, over the next two years, I met with AIDS interest groups and leading AIDS activists, calming their concerns about our test. We formed an advisory group composed of leading AIDS activists, physicians, like Don Francis, and scientists. We received support from minority groups, like NAACP and La Raza.

Leaders in Congress on both sides of the aisle supported our test after I met with them and they learned about our test's potential to save lives. Newspapers like The Los Angeles Times supported home AIDS testing on their editorial pages. And we worked with the states, which reversed their law that banned our test. In short, we gave FDA the political cover they had specifically requested.

So, in 1994, with essentially the same data we brought to FDA in 1987, FDA's advisory committee met and supported approval of our test. The clinics, which feared competition, still opposed our test. So, despite its promise to expeditiously review our application, FDA in the midst of this epidemic took two more years before it ultimately changed some of its criteria, not the ones which restrict a rapid test, and approved my company's product in 1996. I left the business shortly thereafter. At that

time, there was still strong political opposition to a rapid home AIDS test and FDA had still not changed its criteria that precluded approval of such a test. Ten years have now passed.

Today, FDA is reconsidering its opposition, stating as its reason that, "With improved test kit technology, we --

[Announcement.]

Okay. You all can read it. "With improved test kit technology, we believe it may be feasible to identify regulatory criteria for home use HIV test kits."

The real reason FDA's position has softened is a warming political climate, not improved test kit technology. FDA's ban, not a lack of technology, is --

[Fire alarm test.]

The real reason FDA's position has softened is a warming political climate, not improved test kit technology. FDA's ban, not a lack of technology, is the reason no company has approached FDA seeking approval for a home AIDS test before now. Major health care companies are well aware that FDA has had a longstanding bias against home AIDS tests.

Let me provide perspective. In 1994, my company, by that time a Johnson & Johnson subsidiary, had developed a rapid home use HIV saliva test, which had cost and

performance characteristics as good or better than the rapid tests available today. We did not seek approval because FDA made it clear they would not even consider an application. An entrepreneur can afford to fight FDA. A large company with a diverse product portfolio is afraid to antagonize the regulator of its pipeline.

I have no doubt there are companies with strong development and manufacturing expertise which have proven consumer marketing and distribution capabilities that could enter this arena with even more effective and efficient products than we had in 1994. They must be encouraged to do so.

For 20 years, devoid of data, FDA invented the theoretical risk of suicide to do the bidding of AIDS activists and competitors of home tests, testing clinics and labs. When politics isn't its guiding light, FDA relies on science. Last month, for example, an FDA advisory committee recommended a black box warning label on stimulants. The New York Times reported, "FDA officials said that warning patients about a theoretical risk might scare many away from needed treatment. We still believe that what you tell people should reflect the available data, said Dr. Robert Temple, director of the agency's Office of Medical Policy." FDA's mandate is clear: to be above politics and make life affecting decisions based on

data, not unsupported theories.

Yet at today's meeting, FDA is still raising baseless theoretical risks it claims are associated with home AIDS tests. Home AIDS testing can reduce the spread of infection, both from the 25 percent of those HIV infected Americans who don't know it and are infecting others, as well as from the alarmingly high number of those infected with HIV, who know they are infected and don't tell their sex partners.

More than a million Americans have become infected with HIV while FDA has raised the unsupported concern that home testing will lead to suicide --

[Fire alarm test.]

So, while FDA has been raising these unsupported risks of suicide and an increase in risky behavior, a million Americans have become infected. In fact, CDC data and Bernie presented this at your last meeting reveal it is safer to just test and know your partner's status, even taking into account the window period inherent with any HIV test than to just rely on condoms.

So, the safer sex is sex with testing. Yet, FDA has allowed condoms to be promoted as safe, despite their limitations, while contending with no scientific basis that home AIDS tests are too dangerous to allow on the market. We need both in our arsenal to fight AIDS.

Having served in the U.S. Public Health Service, I know that most people in public health, including those at FDA, care deeply about doing the right thing for America. The political climate for home AIDS testing is warming. Yet FDA continues to raise baseless risks about home AIDS tests and sweep the true history under the rug. FDA must take affirmative actions to provide Americans the choice of a home AIDS test and send a clear message to industry and consumers that it is ready to regulate home AIDS tests based on science, not politics.

Thank you very much for your time.

DR. DiMICHELE: Thank you, Mr. Millenson.

I would like to invite Steven Jackson, Mr. Steven Jackson, to the podium and just so you know, Dr. David Resnick will be next.

MR. JACKSON: Good morning and thank you. My name is Steven Jackson and I am the counseling and testing program manager for the Nebraska Health and Human Services HIV Prevention and Ryan White Program.

I would like to thank the FDA and members of the Blood Products Advisory Committee for allowing me time today to discuss this important topic. The Nebraska Health and Human Services system HIV Prevention Program's vision and mission is to lower HIV infection, illness and death rates for healthier Nebraskans and to create an environment

of leadership, partnership and advocacy, which fosters HIV prevention and the provision of services.

NHHS strongly believes in providing options to individuals, wishing to take control of their health care, especially when it comes to learning one's HIV status. At NHHS, we provide both traditional HIV testing and as well as rapid HIV testing in a variety of venues to provide our clients with as many testing opportunities as possible. With HIV testing, our goal is to ensure as many people have access to HIV testing services as possible and that they learn their HIV status.

Despite our best efforts, we know there is a large proportion of people in our state that do not know their HIV status. Because we are a rural state, many individuals do not have easy access to traditional HIV clinics or physicians offices. Also, for those who do have access, it may be that some do not feel comfortable coming to public health settings to seek testing services.

An over-the-counter rapid HIV test would ensure that people in our state have as many options available to them as possible when seeking HIV testing services. It is possible that through an over-the-counter test more people could come to learn their HIV status. We have been using OraQuick for several years now. OraQuick is both easy to use and simple to interpret.

The sample collection is a simple swipe, one time at both the upper and lower gum lines, insert the test device and develop our collection solution and wait 20 minutes. The result interpretation is also simple. One line and you are negative; two lines and we need to conduct additional testing.

Our clinics have had tremendous success using OraQuick. In 2004 with traditional testing, we tested approximately 7,800 individuals in the state. We identified 40 HIV positive individuals of which 20 were newly diagnosed. At that time, our positivity rate was .5 percent. In 2005, we implemented OraQuick testing with oral fluid and were able to provide 8,600 oral fluid rapid tests. The number of positives identified increased from 40 to 53 and we increased the number of newly identified positives from 20 to 42.

The statewide positivity rate increased from .5 percent to .6 percent. The overall specificity for 2005 was 99.9 percent above OraQuick's average specificity claim of 99.8 percent. Our positive predictive value with OraQuick was over 96 percent, which is impressive for a state with a lower seroprevalence rate.

It is my feeling that the simple, non-invasive test directly resulted in our increase in testing numbers, increasing positives was identified and most importantly

the increase in the number of newly diagnosed positives. Although the technology is sound and easy to use, several components would need to be in place to ensure success in an over-the-counter product. The first is an effective counseling message. The face of traditional HIV counseling has been changing over the last several years due in part to advancement of HIV testing technologies and due in part to therapies that are now currently available, which allow HIV infected individuals to live longer, healthier lives.

It is my understanding from OraSure's presentation to the BPAC on November 3rd that the company would provide multiple options for clients to receive counseling that include literature, phone and web-based components. This is a good start, ensuring many options are available for clients. It would be beneficial for the company to work closely with city, state and county health departments, as well as AIDS service organizations to assist in developing this message.

The messaging should be easy to read and comprehensive taking into account the new guidelines the Centers for Disease Control and Prevention will finalize later this year. The post-test counseling message will be the most critical component of an OTC test, especially for individuals who receive a reactive test result. Ensuring these individuals have ready access to information

informing them about the meaning of their results is critical.

Additionally, a system could easily be put in place to assist in linking clients to clinics through a comprehensive database system or even through a state AIDS hot line. This is critical as it is only through confirmatory testing that these individuals will be reportable and can receive access to medical services. I would encourage the company to work with public health in the development of these systems and messages.

Simple, yet comprehensive test instructions would also be needed. These instructions may read from a sixth to an eighth grade level and should be available in multiple languages. Instructions would include how to collect an accurate sample, processing the test, test interpretation, what their test result means, the window period and the next steps to be taken if they receive a non-reactive or a reactive result.

An over-the-counter test will provide people with more options when seeking HIV testing. It is critical that the FDA understands this. Clinical trials should not be designed to impede this advancement, but to ensure that users are informed and comprehend the proper usage of the test, the meaning of the results and additional steps to be taken if needed. An OCT test has the potential to allow

more people access to HIV testing and ultimately provide more individuals knowledge of their HIV status.

Thank you for your time.

DR. DiMICHELE: Thank you, Mr. Jackson.

I would like to invite Dr. David Resnick to the podium and he will be followed by Ms. Fiona Campbell.

DR. RESNICK: Good morning. To all interested parties, my name is Dr. David Resnick and I serve as chief of the Dental Service and founder/director of the Oral Health Center at the Infectious Disease Program of Grady Health System in Atlanta, Georgia.

The purpose of the statement is to urge BPAC and the FDA to support the availability of an FDA-approved rapid oral fluid HIV screening test for over-the-counter use. In an attempt to convey a bit more about my interest in supporting this issue, I am a member of Emory University's School of Medicine, Division of Infectious Disease Faculty, founder of HIV Dent(?) -- a non-profit committed to assuring access to high quality oral health care services for adults, adolescents and children living with HIV disease and the first dentist to be named a member of the core faculty of the International AIDS Society, USA.

Through HIV Dent, I have had the honor of working with numerous organizations around the country, providing technical assistance for the provision of comprehensive HIV

care and treatment. I am here today representing the views of one America's largest public health hospital systems, the Grady Health System in Atlanta, Georgia.

I am of the opinion there is ample data today to support the broad availability of the new rapid HIV test technology. This technology has been FDA approved since late 2002 and was granted a CLIA waiver by President Bush in 2003. Since then more people than ever are learning their HIV status and receiving prompt treatment as a result of the simple, highly accurate rapid HIV test.

For many residents of the United States that are unaware of their HIV status, providing access to this technology over-the-counter would remove some of the barriers to HIV testing. Studies have shown that many who test positive for HIV infection via today's standard of care do not return for their results. Studies have also shown that once a person is aware of their status, if positive, they are up to 70 percent less likely to engage in behaviors that could place themselves and others at risk.

Also, recently published research by Dr. Michael Sagg(?) in clinical infectious diseases has documented that early entry into care and treatment leads to better outcomes and is more cost effective. As a dentist who began my professional career in the private sector in Atlanta, Georgia, at a time as the HIV/AIDS was beginning to

devastate people's lives, I am very aware of the negative effects of stigma and the psychological burden that can be associated with this disease. Therefore, I believe it is in the best interest of those who utilize an over-the-counter rapid HIV test to have access to a complete and effective response system. Key components that should be studied include a 24/7 telephone and Internet-based response system to answer any questions or concerns, both pre and post test.

The system should also contain a centralized resource list of available public and private primary care providers, AIDS service organizations and follow-up to appropriate confirmatory testing and care. Much of this information already exists, such as the American Academy of HIV Medicine's list of providers, which can be accessed by zip codes. Numerous states and territories have compiled a list of available HIV-related services that would be beneficial in the case of a positive result.

I have provided treatment and care for people living with HIV and AIDS for over 20 years. I still witness a significant percentage of our new patients presenting to our clinic with advanced HIV disease. I fully support any effort that will help our citizens learn their HIV status and enter into care at an appropriate time.

I look forward to the day when HIV is no longer devastating our families, our friends and our loved ones. Learning one's status is the first step towards ending this epidemic. I welcome the opportunity to assist you in this dialogue going forward and ask that a copy of my remarks be entered into the record.

Thank you.

DR. DiMICHELE: Thank you, Dr. Resnick.

I would like to invite Fiona Campbell, Ms. Fiona Campbell to the podium. She will be followed by Dr. Steven Lee.

MS. CAMPBELL: Hello. My name is Fiona Campbell and I am an employee of Trinity Biotech. My position covers clinical and retrophase as it relates to new product introductions.

Let me first tell you a little bit about Trinity Biotech. We as a company have been commercializing HIV tests for more than 12 years. We were established in 1992. In the last year alone we estimate that over 7 million persons have been tested for HIV on Trinity Biotech's rapid HIV products. We have several different formats of products on the market at the moment. These products use rapid testing for different technologies, but in the main are based on -- membrane -- technology or latex agglutination technology.

We have a product that is PMA approved at the moment, which is the UniGold Recombigen HIV test. That was approved in December 2003. At that time it was approved for serum, plasma and venipuncture whole blood. The following year, we put a supplement to the FDA and it is approved for finger stick whole blood. Also in 2004, the product was CLIA waived for use with finger stick and venipuncture whole blood.

At this current time, there are many FDA OTC products that use whole blood for qualitative and quantitative analysis. Glucose tests are one of the most common of these tests with millions of home test users in the U.S. taking blood samples everyday. I believe the blood -- have not been at issue here. It is my understanding at this time that sample types approved by the FDA for qualitative analysis for OTC home use are limited to whole blood, urine and stool.

There is currently a home sample collection kit currently approved by the FDA. This kit collects whole blood sample on a membrane, which is sensed by the home user for HIV analysis. There seems to be a perceived concern about biohazards conditions, that sharps need to be involved. Well, they don't necessarily need to be involved in that safety retractable single use lancet shall be provided and also the disposal of residual blood may be

done safely and provide containers and sealable backs. The CDC have also produced a clear fact sheet and entitled HIV and Its Transmission.

Here it states that the virus does not maintain its effectiveness outside of the host. With regard to transmission of risk, if the HIV positive person is performing a HIV home test, the risk is already within the home. The UniGold Recombigen HIV product is a very simple product to use and simply a sample is taken from the finger. It is added to the sample port. Four drops of the wash buffer is then added. You usually only have to wait to ten minutes before results can be read. We propose to provide a timer with the test, which will alert the user as to when they should interpret the test. Trinity will work with the FDA to generate an acceptable means of communication messages to the user.

Here is UniGold's product. As you can see, there are actually two in-built controls with the product. There is a functionality control, which is at the control line in the product. Just cite the word "control." There is also a sample addition control, which is that the sample pores must be a full red color to show that the sample has actually been fully added to the test.

On the test principals and performance data of UniGold's product, I would like to let you know that

UniGold Recombigen test is actually based on third generation Eliza technology. This enables the test to detect IGM in addition to IVG and hence the ability of the test to detect antibodies earlier in the seroconversion phase.

Here presented is the product sensitivity and specificity data, which is generated to support our PMA approval. This data is that which was presented by Dr. Cowan earlier and as Phase I data. You can see that the sensitivity data here, which was actually evaluated at two settings in three locations, where thousand known HIV positive persons were tested in addition to a thousand persons of unknown HIV status in a high risk population.

Of this latter sample set, 32 were positive. All of the samples were correctly identified as -- positive and as later confirmed by EIA and Western blot. The specificity of the product was evaluated in two settings, a high -- setting, where HIV positivity rate was greater than 1 percent and then this was an STD clinic.

The other setting was a blood bank where persons routinely presenting to give blood were tested by the UniGold test. This was considered a low risk population. We also presented significant data on performance of seroconversion panel and low titer panels and the product performs comparably to licensed EIA tests.

Further data that was presented to the FDA was CLIA waived -- from CLIA waiver data was -- flex study data. This included the testing of a blinded panel of samples by a hundred different untrained users. This panel consists of six samples that were blinded. In addition, 60 untrained persons interpreted the results of eight different UniGold tests as presented on picture cards.

To summarize I would like to make the points that the focus of the presentations to date have been focusing on oral fluid as the sample of choice for doing a home test. I would like to make the points that the OTC use of whole blood is established at this current time and that many whole blood samples are taken on a daily basis.

We believe that the UniGold Recombigen HIV test is a suitable format for OTC use and that we would like to make the point that Trinity is committed to internationally supporting the use of HIV rapid tests to reduce the spread of HIV.

DR. DiMICHELE: Thank you, Ms. Campbell.

I would like to invite Dr. Steven Lee from OraSure to the podium and Dr. Lee's presentation will be followed by Mr. Wesley Tahsir-Rodriguez's presentation.

DR. LEE: Hello. My name is Steven Lee. I am the chief science officer for OraSure Technologies and I would like to present some information on the OraQuick

Advanced HIV 1-2 Antibody Test, which is at least a candidate to take through the regulatory process for over-the-counter approval. I am going to focus exclusively in this brief presentation on the oral fluid applications since at least for this product, that is probably the most relevant for the over-the-counter application.

Our test is a very simple two step procedure to use. You simply swab the upper and lower gums, the outside of the upper and lower gums one time each with the flat pad of the test device and then simply drop the device into the developer vial containing developer solution and that is it. You can then read the result within a relatively broad read window of 20 minutes, anytime from 20 to 40 minutes after you do that.

The test also has a very simple result interpretation. Basically one line is negative result. Two lines represents a preliminary positive. It is preliminary positive in the sense that this is obviously a screening test. So, a positive result needs to be followed it with a confirmatory test in order to definitively resolve serological status.

Word on the control line, the control line, which should be present in every test result, if the test has been carried out correctly, indicates that sample containing antibody has been added, that the sample has

progressed beyond the test zone and that the -- you get is active and then if in addition, the test line is reactive, that indicates the presence of anti HIV/AIDS antibodies and is a preliminary positive result.

The test has FDA approved performance claims, oral fluid with a sensitivity of 99.3 percent with confidence intervals of 98.4 to 99.9 and specificity of 99.8 percent with confidence intervals of 99.6 to 99.9 percent. So, this performance is highly comparable to HIV tests using blood and plasma.

We have also had an opportunity to get a more recent picture of HIV performance data with our product, using really two sources. This is a recent postmarket surveillance work that we have done. The first source was from statewide 2005 performance data, using data from various state and city health agencies. This represented over 127,000 oral fluid results with an indicated specificity of 99.8 percent . We also conducted our own customer side by side survey of product performance where we actually contacted all of our customers and requested 2005 performance data and so far we have data obtained from 90 customer testing sites, representing over 43,000 oral fluid tests.

Again, the calculated specificity was 99.8 percent. So, the actual field performance in the

customer's hands corresponded directly to the product claim. Obviously, this performance is very consistent with the 2004-2005 postmarket surveillance data that Dr. Branson has presented.

It is important to recognize that as with any diagnostic screening test, false positives will occur and they do. Recently, there were some reports of some excessive rates of false positives at a few sites on the East and the West Coasts that Dr. Branson from CDC reported on. We found it very useful in the course of our investigation to do a very careful statistical analysis of the performance across a large number of customer sites, including those that had reported these high levels of false positive results.

We conducted analysis across 130 sites, including those sites reporting the high levels of false positives. This methodology of analysis is very similar to the one that Dr. Branson presented. We found that almost all of the sites, in fact, were generating a performance that was within expected bounds. In fact, 95 percent were generating a specificity that was within the 95 percent confidence interval of what would be expected. So, that is a result which is exactly what you would expect.

However, there were these particular sites that did appear to be generating levels of false positivity that

were above what would be expected. That indicated that potentially a special cause was operating at those sites. We did also identify as, again, Dr. Branson referred to, that the product lots that were used at these affected sites, were also used by other sites during the same time period with no performance problems.

This was all strongly suggestive that a site specific factor might be affecting product performance at those sites. So, we have continued to work with those sites. Some of those sites are now reporting performance, which is in line with product claims and we are continuing to work with some other sites as well, just as we would, you know, any customer site that reports unsatisfactory performance as part of our routine product support.

The last point I want to make really is just to comment on the suitability of oral fluid as a specimen for HIV self testing. It provides a very simple non-invasive way of collecting sample, which does not involve multiple steps. It also as we have seen provides established clinical performance comparable to blood and plasma testing. There is also some published evidence that users may prefer oral fluid as a specimen type over blood and this is from published studies with the existing product, as well as some independent market research that we had commissioned of potential over-the-counter users.

So, I think it is at least reasonable to suggest that the availability of an oral fluid based test might at least be an additional enabler of yet more wider use of an over-the-counter product.

Thanks very much.

DR. DiMICHELE: Thank you, Dr. Lee.

I would like to invite Mr. Wesley Tahsir-Rodriguez to the podium and he will be followed by Dr. Fran Spielberg.

MR. TAHSIR-RODRIGUEZ: Good morning, everyone. My name is Wesley Tahsir-Rodriguez and I am the director of Health Policy at the Latino Commission on AIDS and I am also the director of the National Latino AIDS Virus Day, which takes place on October 15th. We have used the OraQuick test to do many, many tests of the past three years.

I would like to thank you for the opportunity to testify as the Blood Products Advisory Committee continues its discussion surrounding a proposed over-the-counter indication for rapid HIV testing.

The Latino Commission on AIDS is a national and regional organization dedicated to addressing HIV in the many Latino communities throughout the country. We are here because almost one-half of Latinos who are positive don't even know their status. Our position today is the

same as it was when we were last here, which is that an OTC test, home test, that provides rapid results that is available in any drug store or on line would have direct and indirect benefits that would result in more Latinos knowing their status and getting connected to care.

In addition, the mere fact that the test would be available just as glucose tolerance and pregnancy tests, would help to destigmatize the HIV test. As you know today, the stigma associated with testing is that only bad people get HIV. Men and women who use drugs, who are homosexual and/or who are seen as promiscuous are viewed by most Latinos as the only people at risk for contracting HIV.

Just taking a test is seen in many parts of the Latino community as admission of engagement in bad behavior. Making a simple test that produces rapid results over-the-counter would help to routinize the HIV test.

We all share responsibility for fostering and even encouraging the stigma associated with HIV testing. First of all, many state laboratories make it very difficult to obtain a limited waiver necessary for rapid testing. Some jurisdictions require that a nurse or medical technical technician administer the test only. Others charge an exorbitant fees for those community based organizations that want to offer the test, therefore,

deterring them from doing so.

Still others make the application process needlessly complex. This contributes to the inaccessibility of the rapid test for those organizations that know the communities that they serve best. This patchwork of regulatory requirements only serves to collect revenue for state governments and protect jobs. The requirements have little to do with public health, especially with the enormous investment that has been made in training community organizations to offer testing.

Second, many HIV/AIDS organizations and clinics have made a sizeable real estate and personnel investment in the testing process. The possibility of a home OTC quick test threatens their revenue and grants of their organizations. Many of them will try to block this approval for reasons that may be public health oriented, such as assuring proper counseling and preventing coercive testing, but in reality it turns on financial concerns.

Third, the FDA and CMS have contributed to this mythology that only certain people can perform the rapid test with the licensing requirements and the requirement of control kits. Hundred of thousands of dollars have been spent on these control kits that many in government and industry will tell you are completely unnecessary.

All of these very powerful forces have combined

to make testing something other than routine. They have helped to perpetuate the hysteria that still surrounds an HIV positive test result and helps to reinforce the fear that many Latinos feel in a positive HIV diagnosis.

Still there are legitimate issues that can easily be addressed in any OTC rapid test. First, the package inserts need to be written in very simple language that explains the necessity of a confirmatory test, follow-up medical care and the time lag between infection and the production of an HIV antibody. While our concern is that the inserts be in easy to understand Spanish, other languages are also important for the African and Asian communities. Although Latinos are united by the Spanish language, there are variations by country of origin and even education level.

Illustrations and diagrams would be ideal to ensure comprehension of these instructions. Latinos should be involved at every stage of the development of these instructions to ensure culturally appropriate language is used.

Second, the telephone service that comes with the home kit needs to be comprehensive and available in several languages. We conducted an informal survey of an existing telephone service and found it to be excellent in providing needed referrals, access to medical and mental health care,

the importance of partner notification and the need for confirmatory testing. We have seen it work.

We recommend that some way be found for the company offering the service to obtain a HIPAA waiver from the purchaser that would enable them to contact that person testing positive in some manner that respects privacy but ensures that there is follow-up. We need to think outside the box to make sure that persons testing positive are connected to care. Confidentiality, safety and accuracy must be ensured throughout the entire process.

Third, state and local health departments need information on persons testing positive in their jurisdictions. This can be done through emphasizing that OTC rapid test is a screening device that requires a confirmatory test. Through the confirmatory testing or subsequent medical visits the government can collect the necessary data. The confirmatory test through either a mail-in blood test or a follow-up medical visit is a challenge with the current system and will probably be a challenge with the rapid OTC test.

The advancing HIV prevention initiative of the CDC is also an important step in reducing the number of HIV infections in the Latino community. Testing, condom use, monogamy and abstinence are all critical to lowering the number of new infections. But any testing, whether over-

the-counter or in person, needs to be culturally and linguistically responsive.

The test must also be responsive to the rigid gender roles that impact women and gay men and contribute to accessing care and testing. It must also be responsive to the Latino family realities that often fail the man or woman testing positive for HIV because of the stigma surrounding the HIV test. The test must also be responsive to the immigration realities confronting many Latinos making their accessing medical services, housing, employment and stabilizing their immigrant status more problematic.

The test must also be responsive to the religious context of many Latinos that fosters the stigmatizing of so many behaviors that are associated with HIV.

Finally, your test must be responsive to the sexual silence imposed on so many Latinos, which makes it so difficult for Latino parents to discuss HIV with their children or evenly openly confront homophobia or sexism.

All of these challenges can and must be met by any counseling offered by the company offering home over-the-counter rapid HIV testing in partnership with medical and community based social service providers.

Ultimately, only a relatively small number of Latinos will take advantage of the home OTC test. But for

those persons, we need to respect their choices for home testing and the fact that HIV infection need no longer be a death sentence. By providing a rapid test over the counter we move one step closer to making it clear that HIV is just one more chronic disease, manageable with education and care and preventable with education. It is important to remember that a person's experience with the rapid test must be one of comfort and ease.

Thank you for your time.

DR. DiMICHELE: Thank you, Mr. Tahsir-Rodriguez.

Dr. Fran Spielberg will be next, followed by Mr. Laird Peterson.

DR. SPIELBERG: Good morning. First of all, I would like to thank the FDA for what I think is a very thoughtful and reasonable report specifying potential requirements for the clinical trials. In my few minutes today, I would like to focus on what I believe are some considerations in weighing the public health risks and benefits of the test and how that translates into the required accuracy that will be established in these meetings.

We have talked a lot about what the potential risks are. So, I don't think I need to go into that in any depth, but obviously if the specificity and sensitivity are quite low, then we will have people who are infected and

infecting others, who aren't aware of their status and the negative emotional reaction from people who are given false positive results.

The benefits clearly, we have talked a lot about when more people know their status, you know, there is good data to suggest that they will change their behaviors. There will be decreased incidence and more people who can access early treatment. Some of the data that helped us weigh these risks and benefits come surveys of accessibility of over-the-counter testing among high risk populations. It comes from the experience that we have seen with the home specimen collection kit. It comes from some of the data that I presented at the last BPAC meeting on the self-testing study that I did to get perspective of positive and to look at the potential feasible -- feasibility and sensitivity.

Then it also is important to consider the effective sensitivity of the task. So, I would like to make a few comments about that. I think the bottom line is that if it is the case that in over-the-counter tests results in more people overall learning their HIV status, then the benefits will very likely outweigh the risks.

So, will OTC reach the untested? The two surveys that I quote here were done both on the West Coast, but in different populations in Seattle and San Francisco. In

both of those studies 20 to 24 percent of a population preferred a home test over any other kind of test. The populations that we were looking at here were people attending needle exchanges, bath houses, STD clinics, high risk populations.

It was also found that people who had never tested were significantly more likely to prefer a home test. So, these are people that may not test in any existing clinic site and would test potentially with an over-the-counter test. Also, in the self testing study that I presented data from at the last BPAC, just to reiterate, among these people who were already positive and knew what it was like to get a positive test result, 61 percent said if they had to learn their status again, they would prefer to do it with an over-the-counter HIV test.

If we look to the home specimen collection postmarketing study, even though the use of that test may have been less than we would have liked to see because of cost and other acceptability factors, it was still the case that among the 1,494 positive users identified in that study, 49 percent had never been tested before. So, clearly that test is reaching is reaching populations who aren't seeking testing in other venues. If you look at the survey studies, 20 to 24 times more people preferred over-the-counter testing to home specimen collection testing.

So, I anticipate that the acceptability will be, you know, much greater.

So, in conclusion, I think it is likely that an OTC will reach a substantial number of people with HIV, who have never tested before and who might not seek testing in existing clinic venues. When we are thinking about how accurate the OTC needs to be for the public health benefit to outweigh the risk, it is really useful to consider the effective sensitivity.

I am defining that as the percentage of true positives identified in a population when testing is available. So if you assumed that performance sensitivity is 99 percent for staff testing and 95 percent for over-the-counter testing, if you go to a population where there are a hundred people with HIV, who are unaware of their status and you offer them staff-based testing and only 50 percent of those people accept and learn their status and you compare that to another situation where you have both staff-based testing available and over-the-counter testing available and you get an additional 20 percent to accept testing, then the effective sensitivity of the staff test would be 49.5 percent for staff-based testing in that population compared to 66.5 percent for a system where you have both staff and over-the-counter testing available.

You can see that because the increased

acceptability results in so many more people learning their status that there can be some tolerance for performance sensitivity before the risks outweigh the benefits. I think that is an important point to consider.

So, I see in this guidelines that the FDA is suggesting 95 percent as the lowest confidence interval -- I mean, as the lower end of the confidence interval. And I appreciate that they heard what was said at the last visit. I think that it is very unlikely that people at high risk will have as high performance as trained staff, especially if you get it to the populations that are at highest risk, that may be of lower education and less sophisticated in their ability to perform these tests. In the pilot that we did, we found 95 percent self test sensitivity and that was a pretty diverse group, a lot of substance use, a lot of mental health issues. So, I think that it is reasonable to attain 95 percent, at least point estimate sensitivity.

I do think that if it is set higher, we simply won't have an over-the-counter HIV test. So, you know, in summary, I think for the standard clinical trial for Phase II, requiring the performance point estimate sensitivity, specificity of greater than or equal to 95 percent is reasonable. I do note that on page 9 and 10 under the section, "Interpretation of Testing of Weak Reactive and Negative Specimens and Interpretation of Examples of Test

Results," they actually are recommending for the panels in the Phase II that people are required to evaluate a 98 percent or 99 percent actually concurrent and I don't think that is reasonable. I think the main problem that people have is in interpretation of the test results.

So, in the study that I did we broke out and looked at the ability to perform the test and the ability to interpret the test separately. It really is the interpretation that gets in the way of some people. So, I think that that criteria should be reexamined and it should be brought down to 95 percent as well.

I would also like to say that in considering what should be done in Phase II clinical trials and whether or not Phase III clinical trials should be done, I think that for Phase II clinical trials, it is very important to do the Phase II studies among a broad spectrum of people who might potentially use the test, not people who might potentially use the test if it cost $35 or more, but people who might use the test if it were provided for free because we are going to have to look at whether and how public health should incorporate self testing into their outreach efforts to reach populations who are unaware of their status.

I think that if we do that, if we go to, you know, pharmacies in communities with high prevalence and

outreach venues and Internets with -- you know, for men meeting men who have sex and really hit the populations that are at highest risk that need to be untested and they might take advantage of the test and do the Phase II in those populations, then I actually think that that should be adequate for FDA approval and that the Phase III should be done as postmarketing studies. For the Phase III trials, I think it would be very valuable to do a study that looked at effective sensitivity because ultimately -- and a study that looked at effective sensitivity would be, for example, a randomized trial where in a population you would randomize by day and offer different testing strategies. So, you would really get to see if different people accepted the test, what the relative rates of acceptance, completion of testing, receipt of test result and follow-up for clinical care would be in a real setting.

By doing that you would give the public health community the ability to look at the relative cost effectiveness of providing OTC and adding that to the kind of tests that they offer.

So, thank you.

DR. DiMICHELE: Thank you, Dr. Spielberg, for sharing your thoughts.

I am hoping that you are going to be available during the committee discussions because there might be

some questions for you that we don't have time for right now because you all are trying to do well, I know, but we are doing very badly in terms of time.

So, we are going to proceed now with the next speaker, Mr. Laird Peterson and he will be followed by Mr. Hermes Chan.

MR. PETERSON: Good morning. Thank you for allowing me the time to speak with you today on this important topic.

My name is Laird Peterson and I serve as the chief of staff for Illinois State Representative Larry McKeon. Primary to my commentary on OTC rapid HIV test, I would like to give you some background information on Representative McKeon and myself.

Larry is serving his fifth term as representative of the Illinois General Assembly. He has been HIV positive for 20 years and is the only openly HIV positive gay member of the Illinois Legislature. Larry serves as the chair of the Labor Committee and vice chair of the Housing and Urban Development Committee and as a commissioner on the newly formed Legislative Ethics Commission and the Commission on Discrimination and Hate Crimes.

Several of Larry's top priorities include education, health care and human rights. I have been HIV positive for over 27 years and have been actively working

in the field of HIV and AIDS for the past 14 years. Prior to joining Larry's staff, I served as the director of prevention services for the AIDS Foundation of Chicago.

HIV testing and the provisions of more options when seeking testing is an extremely important topic and it is good that we are having this dialogue today. In the eighties and early nineties, a positive HIV diagnosis was a crippling, life altering event and face to face counseling was a critical component of HIV testing. A positive HIV diagnosis left little hope for those infected.

Since then, more effective treatments have become available that allow people to live longer and healthier lives. Due to these more effective therapies, a positive HIV diagnosis is not the death sentence it once was. Now, the greater danger is not in becoming infected, but rather ignorance of one's own positive sero status.

Each year, 40,000 Americans become infected with HIV. That is approximately 110 people a day. Fifty-five percent of new transmissions occur because of unsafe sex practices by HIV positive individuals who are unaware they are infected. In 2003, the CDC estimated that between 850 and 950 thousand Americans were infected at the end of the year 2000. Approximately 240,000 of those infected were unaware of their positive sero status. In 2005, those numbers increased 24 percent.

According to the CDC, at the end of 2003, between 1.039 million and 1.185 million were infected with HIV, with the numbers of those unaware of their infection increasing to between 250,000 and 320,000. In 2003, the CDC announced its new strategy, advancing HIV prevention. The focus of this strategy was to increase HIV testing, identification of newly diagnosed positives and linking them into care has been a step in the right direction.

Rapid testing has proved to be a great asset in this endeavor. With rapid testing, more people are being tested than ever before. More people are receiving the results and more importantly more HIV cases are being newly diagnosed. Oral fluid rapid testing has had an even more profound effect, providing more options to individuals seeking testing in traditional public health settings.

Even with the increased amount of testing that has occurred since the implementation of advancing HIV prevention and the use of rapid testing technology, there are still a large number of individuals, who are unaware of their HIV status. These persons are reluctant to seek HIV testing through traditional channels. There is still a need in this country for easier access to HIV testing. Although officials in both the public health and private sectors have increased their HIV testing efforts, many Americans are still unaware of their HIV status.

Many people still don't seek testing because they don't want to wait in the public health clinic. Many don't seek testing because they don't want to disclose risk behaviors to their family physicians. Many do not want a blood draw nor the waiting time required for traditional HIV tests. The technology is finally here in a simple to use, oral fluid test that can accurately be performed by individuals with little or no clinical experience.

This has been demonstrated time and time again as over the past year and a half, traditional HIV counselors across the country have taken on the role of clinicians and accurately performed rapid HIV testing in non-traditional settings.

As I mentioned earlier, counseling was a critical component of HIV testing in the eighties and nineties due to the ramifications of a positive test result. As testing technologies and therapies have advanced, the role of HIV counseling has evolved. Persons living with this disease, such as myself and Larry, are living longer because we were better educated about the disease, take better care of our bodies and we utilize newer therapies. In many ways, an HIV diagnosis can be viewed as a chronic infection that must be managed instead of a fatal diagnosis.

Counseling with an OTC product must contain three critical components. The first is easy to read, easy to

use instructions on how to perform the test and interpret test results. The second is a comprehensive counseling message that is provided in simplistic terms in several languages. This would include pretest counseling messages and individualized risk assessment, appropriate post counseling, appropriate post testing counseling messaging, including the need to seek additional testing in the event of a reactive test result.

Finally, the importance of seeking therapy. The third component is assistance in linking a client to appropriate services for confirmatory testing and linking to care. Thee three components must include a method for personal contact with a counselor, who can link them to local health departments or community-based organizations during a difficult time for the consumer of this product. It is unrealistic to expect a company to ensure clients with reactive tests seek confirmatory testing.

However, it is realistic and should be expected that an OTC product provide clients with as much information and assistance to linkages as possible. With an over-the-counter oral fluid rapid HIV test, we will provide more people with options when seeking HIV testing. It is critical that the FDA understand this. Clinical trials and the approval process should not be designed to hinder this advancement but rather ensure that the test

performance is acceptable.

Users are informed and comprehend the proper uses of the test. Users receive appropriate counseling messages. They understand the meaning of their results and have easy access to resources that can aid them in linking to a clinic for confirmatory testing and care. Ultimately an OTC test will allow more people easier access to HIV testing and ultimately provide more individuals with knowledge of their HIV sero status.

Thank you for your time.

DR. DiMICHELE: Thank you very much, Mr. Peterson.

I would like to invite Mr. Hermes Chan to the podium and he will be followed by Mr. Philip Hilton.

MR. CHAN: Good morning. My name is Hermes Chan and I am the president and principal inventors of our current rapid flow through diagnostic -- of Medmira, Canada. I will ensure my presentation will be completed in less than five minutes.

At Medmira, there are two fundamental factors that dictate our decisions in making a -- of our rapid diagnostic -- general public safety and customer value. I want to thank you for this opportunity to share with you some of the information we gathered with our OTC rapid HIV test over the past year in Hong Kong. It is our sincere

hope the committees will take our experience into consideration before making home based rapid HIV test a reality.

Over the past 12 months we have collected information from our end users, who purchased our MiraCare rapid HIV test from their pharmacies across Hong Kong to address four key questions. What do people want from an OTC rapid HIV test? Can they use it properly? Will they use it properly? What will they do with their result? I want to emphasize that this informations were collected from real end users, but not the -- from paper surveys.

While our process in collecting data continues, we have sent requests for a majority of our end users from the method of confirming their results regarding whether they reactive or non-reactive. Five percent of our customers choose not to perform the test until signs of HIV infections appear, which our operators will immediately discourage them and convince them to do the right thing.

About 10 percent of our customers on the other hand are reluctant in using the test and ask if somebody else can do it for them and subsequently they also ask for a refund. On the other hand, about 20 percent of the end users ask about the confirmatory test that they need to go through and where they can go about and confirm their results. As a result, preliminary conclusions, based on

what we have learned in Hong Kong, MedMira believes that a responsible OTC rapid HIV test should provide a means of effective precounseling and instant HIV test results, a means of assessing confirmatory results in private, an alternative to the end user who decides not to do the rapid test or who performs the test incorrectly and finally a means of effective post-counseling and referral to medical care.

I want to -- that we were currently seeking advice from FDA to approve our proposed MiraCare's rapid HIV testing system for home use and we believe our systems can address the concerns of the public.

Thank you very much.

DR. DiMICHELE: Thank you, Mr. Chan.

I would like to invite Mr. Philip Hilton to the podium. The next speaker will be Deanna Sykes.

MR. HILTON: Madame Chair, Abraham Lincoln once remarked that a truly great speaker knows when to sit down. So, I promise you that I will be brief.

Good morning, members of the committee, ladies and gentlemen. My name is Philip Hilton. I serve as senior vice president and as special assistant to the president, chief executive officer of the National Black Leadership Commission on AIDS. Thank you for the opportunity to express our views on the matter before you

today and for your willingness to listen. We are here today with an urgent message of support for the immediate availability of an FDA approved simple rapid saliva HIV test that is made available over the counter. Now, if you will permit me, I would like to take a few moments to brief you on my organization.

The National Black Leadership Commission on AIDS was founded in 1987. Our organization's mission is to inform, coordinate and organize the volunteer efforts of indigenous black leadership, including clergy, elected officials, medical practitioners, business professionals, social policy experts and the media, to meet the challenge of fighting HIV/AIDS in their local communities.

We conduct policy, research and advocacy on HIV and AIDS to ensure the effective participation of our leadership in all policy and resource allocation decisions at the national, state and local levels of government and within communities of African descent nationwide. We are the oldest and largest not for profit organization of its kind in the United States.

We are establishing affiliates in 17 cities throughout the United States, where communities of African descent are hardest hit by the HIV/AIDS epidemic, including Nassau County, Albany, Syracuse, Rochester and Buffalo in New York State, Newark, Philadelphia, Boston, Baltimore,

Atlanta, Detroit, Cleveland, Chicago, Miami, Houston, Los Angeles and Washington, D.C.

We have served thousands of organizations and institutions through community development, technical assistance and formulation of public policy, helped to raise over $1 billion in new federal funding for HIV/AIDS and public health related direct service organizations, serving communities of African descent and created the first program for black clergy to develop strategies to address the complexity of problems caused by HIV and AIDS.

We also serve as chief consultant on HIV/AIDS and public health related issues to numerous national organizations. Among them are our partnerships with the Congressional Black Caucus and our official partnerships with the National Association of Black Social Workers, the National Caucus of Black State Legislators, representing over 500 black state elected officials and the National Baptist Minister's Convention with a membership of 8.2 million.

We have proudly served as an advisor on HIV/AIDS related issues to the United Nations and to the nations of Gabon, Central African Republic, Uganda and the Bahamas, among others. We are led under the direction of Debra Fraser-Howze, who brings more than two decades of personal leadership and experience to this debate. In June of 1995,

Mrs. Fraser-Howze was appointed by then President Bill Clinton to the Presidential Advisory Council on HIV/AIDS. She served on the council until her tenure ended on July 31, 2001. As you may know, the council's mission is to provide advice, information and recommendations to the President of the United States regarding programs and policies to promote effective HIV prevention, advanced research on HIV and AIDS and to promote quality services to persons living with HIV and AIDS.

The council was the first national body established to solely and directly advise a President on this issue. Mrs. Fraser-Howze has been recognized for her local, national and international leadership to communities of color regarding teenage pregnancy, social welfare and HIV/AIDS. Through her advocacy, African Americans and other peoples of color have gained greater inclusion in local and national policy, planning, research and clinical trials.

Her ability to develop solutions and build effective coalitions to address major issues affecting communities of African descent have been recognized worldwide. Her counsel has been sought by governments around the globe. With our base of experience and leadership on the issue of HIV/AIDS in African American and other communities of color, our message on the matter of

whether to support approving rapid HIV testing for home use is: The National Black Leadership Commission on AIDS stands with those, such as the National Minority AIDS Council, the National Association of Evangelicals, our brothers and sisters at the Latino Commission on AIDS and others, who strongly support approval.

There is no reason why empowering Americans for this rapid HIV testing option is not available today. This technology has been available for years in public health communities, hospitals and physicians' offices. It is simple, safe and effective. Those of us in the community, who choose to be empowered to know our HIV status ought to have the ability to do so.

I ask that a copy of my statement be inserted into the public record and I thank you very much to the committee for listening.

DR. DiMICHELE: Thank you very much. Appreciate your words, Mr. Hilton, and you did, indeed, stay on time. Thank you.

Ms. Deanna Sykes, please, to the podium and Dr. Evan Cadoff will be next.

MS. SYKES: Good morning. Is it still morning? Close to it. Good.

Going at this time of day allows me the luxury to skip over some of the things that have already been covered

in depth. So, I will be sure to do that.

My name is Deanna Sykes. I am a research scientist for the California Department of Health Services. I have been engaged for the last three or four years in developing and coordinating the roll out of rapid testing in our public health counseling and testing setting. So, the data and impressions that I am going to offer up today are based on that experience.

We started our implementation back in May of 2003 with the original OraQuick antibody device. We are working in counseling and testing settings and we have our counselors operating the device. The reason that is interesting is because a lot of our counselors are recruited from the populations that we target, you know, injection drug users, sex workers, MSM, et cetera. So, they actually reflect something like what we might want to call -- or a subset of intended users. Our in the field specificity was 99.94, which we were really, really pleased with because not only is that within the manufacturer's specifications, it is actually very much on the high end.

Of course, our counselors did get training. So, that is a little bit different, but we are very pleased with that because our lab folks suggested when we started this project that we might expect our specificity in the field, our accuracy over all in the field to be

considerably lower than what showed up in clinical trials and, in fact, we didn't find that to be the case. I attribute that to the ultimate simplicity of the OraQuick test that we are using.

Being one of the -- Bernie presented a lot of data on the oral fluid kind of fluctuations and being one of the areas that was impacted by that, I wanted to give you a little bit more information. This is a look at our oral fluid data during the time period when the agency in L.A. and a couple of agencies in San Francisco were having a problem. You can see actually that looking at just the agencies or just the rest of California that was not experiencing this problem, specificity with oral fluid was quite high, almost comparable to the finger stick specificity.

Overall, we are well within the manufacturer's claims. What this brings up for me is the fact that the test -- the big issue, you know, it hit the newspapers and everybody got all excited and everything and the big issue there wasn't that we were really having more false positives than expected. It is that they were turning up in clusters. Okay. Well, why is that interesting? Well, based on my interactions with the folks who are having these issues, of course, clients who get a false positive or a preliminary positive result at all go through some

anxiety, but the people who were bothered the most by this were actually the test operators because they were the ones who were having to deal with the cluster issue.

The clients themselves were still only dealing with their test results. Okay? Of course, that will be the same issue for an over-the-counter, the clustering issue, if it continues to occur, won't have the same impact.

A real quick look at benefits and concerns. People have pretty much beat this to death, increased access for hard to reach high risk populations. That is pretty much not debatable. Testing alternatives for low risk populations, this is interesting for us because the funded program that we do primarily is actually a targeted program, where we do a more intensive risk reduction intervention. What happens is that we are inundated with a lot of folks, who basically just want to test and don't really need the counseling and can't get this rapid test in very many places.

So, broader access to it, whether through expanded screening, in medical settings and especially through an over-the-counter use would allow us to focus our public health prevention funds a little bit more effectively. I haven't heard anybody say that yet. Empowering health consumers can't be a bad thing. You have

already heard about how it is likely to destigmatize HIV , which is something that we desperately need to do.

The possible concern that I listed here was the possibility that over-the-counter availability or even broad screening availability may mean that it is harder for us to get some of the people in for a prevention intervention than it is right now, where, you know, we have the carrot of the rapid HIV test to get them to come in. But I can't see in any way how that could possibly outweigh all the benefits that have already been stated. So, I think we are going to have to get creative about other prevention techniques and opportunities with folks who are at high risk.

Finally, I think that most folks have listed these. Obviously, we need to talk about confirmatory testing, window period. I think it would be useful, especially when you consider the idea of folks testing their sex partners, to know that -- for users to know that HIV vaccination can cause false positives, that heart may cause false negatives, in the interest of disclosure.

Finally, other issues. I perused the transcript from the last session and noticed a few issues that people brought up. All I really want to say about this is that if the user instructions do a good job of getting people to access confirmatory testing, the other two issues are non-

issues because they will continue to happen in the same way as they do now. When folks come in for confirmatory testing, they will be into the system where we can work to link them to care if, in fact, they elect to have care and HIV reporting happens on confirmed results as well. So, the over-the-counter application doesn't really impact the second two, as long as the first one is done well.

Final thoughts, just that this test is stunningly simple to use. We have been using the oral fluid version in particular of the OraQuick. It is amazing how simple. I spent about five hours on a plane yesterday on my way here and you know how they have all of those little picture things to show you how to lock the bathroom door and how to, you know, do all that and I was struck by the fact that you could almost put instructions for this test in that sort of a format, not quite, but almost.

Finally, this has been beat on to death, too, accessibility of testing is hugely, hugely important if we are going to manage this epidemic better than we have.

So, thank you very much for your time.

DR. DiMICHELE: Thank you, Dr. Sykes. You are also very much on time. Thank you.

Dr. Evan Cadoff, please.

DR. CADOFF: Thank you.

DR. DiMICHELE: I am sorry. Excuse me one more

second. Mr. Anthony Tran will follow Dr. Cadoff. Sorry, Dr. Cadoff.

DR. CADOFF: In terms of disclosure some of my expenses here have been paid by OraSure. I am a clinical pathologist. I am responsible for HIV testing done at a network of sites throughout New Jersey. We have 138 counselors trained with quite a variety of backgrounds and we operate at over a hundred sites. We have been doing OraQuick since November of 2003.

Just to show that test volumes, HIV testing at counseling and testing centers in New Jersey were declining steadily. It is the blue line over ten years. With the introduction of rapid testing, we saw an increase and we expect that that would increase even more with over-the-counter testing. So, we support that.

We participated in some CDC sponsored studies and we did see when we switched from blood to oral testing as is expected, a slight decrease in specificity, but we did not see a decrease and we looked very carefully at our data and we are using some of the same lot numbers as San Francisco and New York last fall and did not see an issue. I think specificity has been beaten to death. So, with our 138 counselors at 117 sites, it was not an issue and shouldn't continue to be one.

What I did want to address is sort of counseling

issues that relate to over-the-counter approval. That is that the FDA proposal doesn't include a target for counseling. Our sites do report 99 percent of clients who come in to get tested do get pre and post test counseling. However, their funding depends on documenting that their counseling is complete. I know that in some cases when they have counseled 10 patients in an hour and a counseling session is supposed to be 20 minutes, that it is not 99 percent.

With traditional testing, it was acceptable to have a third of the people not come for their post test counseling. I don't know that we should expect over-the-counter testing to have a significantly greater bar than we had accepted for professional use testing.

Also, a non-scientific survey, one of my staff is from an OB, was a nurse in an OB office and from my wife's experience, there was virtually no counseling with HIV testing that is done by the obstetricians, at least in our community and again to require -- you know, just in terms of assessing where the bar should be for the counseling that is assured with over-the-counter product, I think should reflect the reality of what is going on and not the idealized public health setting where we are having people coming in to a counseling and testing center, where counseling is an intrinsic part of what goes on there.

This is not only going to replace that or not only going to be in that market, but in other markets as well.

False positives and counseling for false positives, which is a concern that everyone has related to the nonspecificity issues. It is a rare event for our trained counselors. We have 138 counselors. We have had about 50 false positives in two years. Most of our counselors have never had to deal with the counseling of patients about a false positive and don't know how to do it. So, saying that trained counselors are better at that than in certain materials in an over-the-counter product is not necessarily true either.

So, again, the trained counselors are uncomfortable and don't necessarily have the resources that they need at the counseling centers to do that and, again, I think that something at least equivalent should be able to be provided in an over-the-counter product. Also, I think that clinicians need assistance. I think some people will now go directly to a practitioner, who until rapid testing came around, has never had to deal with an unconfirmed preliminary positive result.

Traditional HIV testing done by any clinician going through a laboratory, a reference laboratory, that result is always confirmed before it is reported so that the clinicians do not have the background to do that. So,

perhaps as someone suggested at the last BPAC meeting, there should be an insert in the kit for someone to take to their doctor if they are going to their doctor to get a preliminary positive confirmed.

So, the target, the target, the goals for what counseling, the level of counseling that the vendors should need to prove should be substantially equivalent to actual current practice and I don't think should be set at an artificially high level. The FDA has not proposed a specific level. I would like to encourage that it be a realistic one and not an unattainable one because we don't want it to prohibit approval of over-the-counter sales.

I would like to address some issues with the caution of exempting these from reviewing the Phase I trials that were submitted if we go to over-the-counter. I guess it sounds fairly clear to me that false positives due to oversampling do occur and the flex studies in the Phase I talk about investigating oversampling. Having thought about this, I don't know that we should suggest that that be done because we certainly don't want to suggest to people don't over sample because then they are going to do it. So, if we are not going to do anything about what happens if they over sample, other than addressing false positives, I don't know that -- I guess it is necessary and they should just avoid that.

But one of the things that I am concerned about is high storage temperatures and perhaps the flex studies relative to the temperature stress may need to be repeated over the counter because we saw a cluster of false positives that we don't have hard evidence for but were done at one of our sites that had less than optimal control over the storage of their devices and our suspicion is that that cluster of three false positives that were done at simultaneous tests -- they did four tests. Three of them were falsely positive, confirmed with one month follow-up that they actually were false positive and we think that those devices may have been stored improperly and that may have led to this false positive phenomenon.

We know that last November about the time of the BPAC committee, OraSure did shorten the shelf life on their existing kits because they had a problem with false positives occurring with high temperature storage. So, I wonder whether that flex study shouldn't be exempted for over-the-counter use because those stresses may not be the same over-the-counter leaving the kid in the back of the car as they are in professional use.

So, in summary, over-the-counter use would increase knowledge of HIV status, which is an important goal. Specificity I think is proven is not really an issue. Evaluation of over-the-counter -- OTC counseling

should be equivalent to typical current practice, not an ideal practice and perhaps the flex studies for temperature sensitivity should be reexamined or the criteria changed.

Thank you.

DR. DiMICHELE: Thank you, Dr. Cadoff, for those important points.

I would like to invite Mr. Anthony Tran to the podium, please and he will be followed by Mr. Paul Lakoskey.

MR. TRAN: Dear Blood Products Advisory Committee, on behalf of the Association of Public Health Laboratories, APHL, I am writing to provide comments to the Blood Products Advisory Committee, BPAC, and Food and Drug Administration, FDA, regarding the criteria and questions that need to be addressed prior to an OTC home use rapid HIV screening test indication is considered.

The APHL membership consists of state and local public health laboratories, whose primary responsibility is to conduct testing of public health significance for the purposes of surveillance to protect the nation's health. APHL with a history of over 50 years is dedicated to working with its members and the health care community in general to strengthen public health laboratories by striving to provide the necessary resources and infrastructure.

The public health laboratories have been on the forefront of HIV diagnostics and testing ever since the discovery of the disease in the early 1980s. Public health laboratories provide screening and supplemental testing for confirmation of HIV for state and local jurisdictions. They were instrumental in assisting the Centers for Disease Control and Prevention, CDC, with developing the current testing algorithm for HIV.

APHL also has a position statement on the suggested use of rapid HIV testing in certain settings. The complete APHL position statement can be found at www.APHL.ORG.

Rapid HIV testing has been demonstrated to be an effective tool for HIV diagnosis. However, this is only one step in a process that includes counseling, supplemental testing for confirmation, referral to medical care and access to treatment. APHL is concerned that over-the-counter home use HIV testing will not provide adequate assurances for these steps, thus negatively impacting the individual patient, as well as public health surveillance and control measures.

Currently, there is insufficient data for APHL to either support or oppose the concept of an OTC home use rapid HIV screening test or any specific test that may seek over-the-counter status. The BPAC meeting held November

3rd, 2005 helped answer some of the questions necessary for APHL to consider. However, it brought up several others as well. Studies suggested by the BPAC will be instrumental in providing the required information so that APHL and other organizations can determine their stance on over-the-counter HIV tests. The following questions outline the additional information that APHL will need in order to take an informed position on an OTC home use rapid HIV screening test.

1. How will OraSure Technologies and other companies seeking OTC status ensure that proper quality assurance and proficiency are maintained with an over-the-counter home use rapid HIV test? Many states and local jurisdictions that offer the rapid HIV test in their community require counseling and testing sites to undergo extensive training and education prior to these sites administering the test.

Will there be any measures contained in the test kit that will ensure that individuals are properly utilizing and interpreting the test?

What documents in support will be supplied to ensure that the test is being performed and interpreted correctly?

2. What further analysis and support will be documented to ensure that product will perform as required

after exposure to adverse climate conditions outside the limits as described in the package insert. Laboratorians are well aware that summer and winter weather can adversely impact the performance of a test kit.

Systems are in place to care for the product from the loading dock through use.

Are retails able to provide special handling to protect the test kit? A product that will now go through a secondary transport to the end user's home is not controlled and may impact the result. Therefore, exposures of extreme temperatures and humidity must be validated.

3. What validation studies will OraSure Technologies and others develop in order to assure that the study population mimics that of the general population that we utilize the test? It is important that studies of test performance conducted by OraSure Technologies and others be done in the population intended to use the test. It is currently not clear what that population is, i.e., who is likely to buy the test? College graduates, high school students, homeless people, Medicare recipients, et cetera?

4. How will individuals who test reactive or preliminary positive be referred for supplemental confirmatory testing? The OTC home use HIV test will act only as a screening tool for HIV infection. Supplemental testing to confirm the presence of HIV antibodies will be

required. How does OraSure Technologies and others plan on ensuring that all individuals with reactive or preliminary positive results from the OTC rapid HIV test receive a supplemental confirmatory test?

5. How will OraSure Technologies and others make certain that those individuals who test reactive or preliminary positive are referred into counseling and medical care? Data provided at the last BPAC meeting by Dr. Enungoo(?) at Central Michigan University indicate that discrepancies exist with regards to how a reactive or preliminary positive HIV test result impacts an individual's distress level. Traditionally a counselor or physician is on site to provide the counsel and defer the individual into treatment and care.

A supplemental specimen may also be obtained for confirmatory testing during the initial visit. What protocols will be in place to ensure that all individuals receive the same care?

6. What measures will be in place to prevent the bulk sale of an over-the-counter home use rapid HIV test to entities attempting to establish themselves as a counseling and testing site? To maintain a high quality of testing health departments and public health laboratories want to be able to continue any existing roles in overseeing counseling and testing sites that offer rapid HIV testing.

If bulk sales are allowed, then it would circumvent this process.

7. How does OraSure technologies and others plan on addressing state and local mandates that either require the presence of a physician or do not allow for the sale of rapid HIV tests? There are some states and local jurisdictions that have these types of requirements. What precautions will be taken to prevent individuals from purchasing an over-the-counter home use rapid HIV test from another jurisdiction and bringing it over the border?

APHL appreciates the opportunity to react and weigh in on this very important issue. We realize that an OTC home use rapid HIV would allow for many more individuals to be tested for the disease in the United States and potentially seek care. APHL does, however, have concerns and anxiously looks forward to hearing additional information about how OraSure Technologies and others plan to address these issues.

The required studyshould address many of these concerns and potential conflicts with the policy or mandates may still exist. The CDC, FDA and other federal agencies will need to work with APHL and other partners to address these policy issues as well.

Thank you for your time and consideration. Best regards, Scott Becker, Executive Director, the Association

of Public Health Laboratories, and Jane Getchell, Director of Delaware Public Health Laboratory and Chair of the APHL Infectious Diseases Committee.

DR. DiMICHELE: Thank you, Mr. Tran. I'd like to invite Mr. Paul Lakoskey to the podium. Mr. Lakoskey's presentation will be followed by Dr. Douglas White. I just want to ask again, we still have almost a half a dozen speakers and we are way over time, and I'd like to hear all of your voices but the committee will still need time for deliberation, so as briefly as you can make your presentations, please do so. Thank you.

DR. WONG: Hello, good morning. I am not Paul Lakoskey. My name is Dr. William Wong. I am substituting for Paul Lakoskey. He is director of capacity building with the Chicago Department of Public Health.

Again, my name is Dr. William Wong. I am medical director with the STD Prevention and Care Program for the Chicago Department of Public Health. As a point of disclosure, I do not have any financial interests in any HIV testing manufacturer, and I have not received any payment for this statement.

I would like to thank the FDA and members of the Blood Products Advisory Committee for allowing me time today to discuss this important topic. The mission of the Chicago Department of Public Health Division of STD

HIV/AIDS is to work in partnership with the community to use the best public health practices for the prevention and treatment of HIV and sexually transmitted diseases, and to promote the highest quality services for the health and well-being for those living with and impacted by STDs, HIV and AIDS.

The Chicago Department of Public Health strongly believes in providing options to individuals wishing to participate in their own health care, especially when it comes to learning one's HIV status. At CDPH, we provide both conventional HIV antibody testing as well as antibody testing using HIV rapid tests in a variety of venues that range from public health clinics to community-based organizations to mobile testing vehicles and to other outreach settings. With HIV testing, our goal is to insure that as many people have access to HIV testing services as possible, and that they learn their HIV sero status.

The Chicago Department of Public Health participated in CDC's postmarketing surveillance project as one of its 17 sites. Despite our best efforts, we know that there is a substantial portion of residents in the city that do not know their HIV status. Perhaps some do not feel comfortable coming to public health settings to seek testing services. Perhaps some don't feel comfortable asking their physician or health care provider for an HIV

test. Whatever reason, we believe that a simple to use over-the-counter HIV rapid test will provide people with more options when it comes to seeking HIV testing, and could result in more people learning their HIV sero status. This will expand testing to reach populations who ordinarily would not get tested.

We have been using OraQuick for over three years now. OraQuick is both easy to use and simple to interpret, and our program has had great success in using OraQuick. In 2005 we performed over 8100 HIV rapid tests in clinic and community settings. Prior to implementing HIV rapid testing, 70 percent of the patients who were tested for HIV using the conventional HIV antibody test actually returned for HIV post test counseling to receive their test results. That is, about 30 percent of people who were tested for HIV using conventional HIV antibody tests never found out their HIV test results. The percent of patients who received post test counseling improved greatly after we implement the HIV rapid testing program.

In 2005, over 99 percent of people who took the HIV rapid test received their HIV test results. Furthermore, compared to conventional HIV antibody testing, HIV rapid tests identified a higher percentage of HIV positive persons. The positivity rate of conventional HIV tests was 0.9 percent in our clinics in 2005, compared to

the positivity rate of HIV rapid tests of 1.6 percent, almost double. More positives are being identified through the use of this simple, quick, non-invasive test.

The specificity of OraQuick has been equally as pleasing. The manufacturer's labeling calls for an average specificity of 99.8 percent. In 2005, we experienced an overall specificity of 99.9 percent, with only six confirmed discordant test results. Further sub-analysis demonstrates excellent test performance characteristics. The specificity was 99.90 percent on oral fluid and 99.97 percent on whole blood. HIV rapid testing has been so successful that in 2006 we plan to expand the amount of rapid testing conducted in the city by 25 percent.

Although the technology is sound, the test easy to use and the results accurate, several components would need to be in place to insure the success of an over-the-counter product.

The first is an effective pretest counseling message. I understand that Orasure's presentation to BPAC in November described the plan to provide multiple options for clients to receive education and counseling. That includes literature, phone and web-based components. It would be beneficial for the company to conduct focus groups with city, state and county health departments, as well as AIDS service organizations, to assist in developing these

messages. The messages should be comprehensive and easy to read, taking into account the new guidance on HIV counseling and testing the Centers for Disease Control and Prevention will announce later this year.

Second, the post test counseling message is the most critical component for an over-the-counter test, especially for individuals who receive a reactive test result. Insuring that these individuals have ready access to the information needed to inform them of the meaning of their result is the most important part of the post test counseling session. A system could easily be put in place to assist in linking them to clinics and health care providers who can provide the additional counseling and/or confirmatory testing. This is critical, as confirmatory testing will allow surveillance reporting and facilitate partner notification and partner counseling and referral to insure that individuals can access medical care to life-saving therapies. I would encourage the company to work with public health departments in the development of these messages.

Third, another component essential to a successful over-the-counter rapid test is insuring that proper quality control mechanisms are in place so that the test is not compromised prior to or during use. Climate conditions that may affect the test could be monitored with

a climate sensitive panel affixed to the outside of the box. If the test is exposed to extreme temperatures, humidity or light conditions that may affect test performance, this panel could change colors and notify the customer. Clear language on the outside of the packaging would inform the individual what the color coding of this panel means. Additionally, the product expiration date should be clearly labeled on the outside of the package.

Finally, simple yet comprehensive instructions would also be needed. These instructions should be at the sixth to eighth grade reading level and should be available in multiple languages. These instructions should include how to collect a proper sample, how to process the test, test interpretations, what their test results mean, the window period and next steps to be taken if they receive either a nonreactive or reactive result.

An over-the-counter test will be a huge benefit to public health. If done properly, it will allow more people to have access to HIV testing, and will provide more individuals knowledge of their HIV sero status.

Thank you for your time.

DR. DiMICHELE: Thank you, Dr. Wong. I'd like to invite Dr. Doug White to the podium. He will be followed by Dr. Richard Rothman.

DR. WHITE: My name is Douglas White. I am an

emergency department physician from the Alameda County Medical Center, Highland Hospital, which is located in Oakland, California. My goal today is to give you a clinical perspective of what it is like to implement a rapid HIV test in a large scale clinical experience. In the full interest of financial disclosure, I have spoken before for both Abbott and Orasure, and they invited me to speak today. I have received compensation only for travel, and I have never received monetary compensation for speaking engagements.

We all know about the worldwide epidemic that HIV is. I think it is clear that we know that we are not immune to this here nationally, with over a million people infected, a quarter of the people unaware, and all of the barriers to HIV testing that were present years ago are still very much on the forefront today. Accessibility, fear of getting a test, the stigma, confidentiality issues as well as cost issues prevent people from getting tested, and the inherent nature of conventional testing which requires patients to return in a week, sometimes two weeks, for the disclosure of their results is clearly a major barrier.

Rapid testing is one solution to overcome some of these barriers. It is very obvious to me in my daily practice that by offering a rapid test, patients take you

up on it. They are very much like emergency department physicians; they want answers now. Patients really don't want to wait two weeks. If you give them the option they will pick the rapid test almost every time. Clearly with results being ready in minutes essentially, nearly everyone who gets tested is disclosed their results.

There is also a portability function that the rapid test affords. This enables us to test in our emergency department. It enables testing in nontraditional outreach centers. It enables testing in Third World countries where it wouldn't traditionally be performed. You can see how this could apply to the outpatient over-the-counter setting, where someone could test in the privacy of their own home if they choose to do so.

Highland Hospital is your standard urban academic teaching hospital which is publicly funded. Our emergency department serves as the regional trauma center. We have a full-scale emergency medicine residency. We have over 70,000 patient visits a year. We serve a diverse and indigent patient population. This is basically a stressful center, and you can imagine trying to integrate rapid testing into the daily operations of an ED. Many people thought this was an impossible undertaking.

I am the project director for a two-year CDC funded feasibility project. The goal of our project that

we have implemented a little over a year ago was essentially to routinely offer a rapid HIV test as a routine part of the daily emergency department operations. We have succeeded in doing this by simply offering the HIV test to every eligible patient that comes through our triage area.

Our triage nurse offers the test to everyone who comes through triage. If a patient wants to be tested, their medical chart is flagged as a patient who desires testing, and the test is then performed at the patient's bedside. Our nursing staff does essentially everything. They perform informed consent, they perform the test, they interpret the test and they disclose all negative results. It is the role of the emergency department physician to disclose the preliminary positive results and link that patient to care.

We have a protocol in place that every patient that has a preliminary positive test will be linked as soon as possible to one of two outlying HIV clinics. In order to accomplish this large scale testing protocol and not disrupt the daily operations, we have an incredibly streamlined testing and counseling protocol. We rely heavily on the provision of preprinted written materials to educate patients and to use in our disclosure of negatives. We really focus our efforts on the disclosure of those few

patients that have preliminary positive results.

We use exclusively the OraQuick advanced test using oral fluid, and we have no experience using an alternative rapid testing device. I chose this particularly because we could use it with oral fluid, and I had done a pre-study survey of patients as well as nursing staff, and it was nearly unanimous that if you had the choice, they would choose oral fluid.

So we have had quite a bit of success, I believe, in the first little over a year in the implementation of this particular project. We have tested over 6,000 patients, which represented approximately eight percent of our first year census in our emergency department. We have had 84 reactive tests, and 82 of those were confirmed with western blot. That means we have had two false positives. One of those had an indeterminate western blot and a negative IFA, the other had both negative World Bank and negative IFA. We have had one false negative, which occurred in a patient who clinically had end stage AIDS by clinical stigmata, who we had such a high clinical pretest probability that we tested him with blood analysis and did viral loads, and on subsequent repeat oral testing his second oral test was preliminary positive. That was felt to be due to provider error in interpreting the test at the bedside.

We have an 83 percent followup rate, which means that patients who are disclosed to have a preliminary positive result in the emergency department setting actually made it to at least one or more followup appointments at an HIV clinic.

Patients are incredibly satisfied with this procedure. This is data from patients who have newly diagnosed positives; 96 percent rated their experience as either good to excellent, and only four percent rated it as poor. The majority of patients would recommend an emergency department setting as a place to come and get a rapid test.

So I feel that routine voluntary HIV screening in nontraditional settings such as a busy emergency department is a feasible undertaking. I feel strongly that the particular product that we have used, OraQuick Advance, specifically using oral fluid testing, is very simple and very easy to use. I have over 120 nurses out there doing this test. Some are fulltime employees, some are one-tenth employees, some are traveling nurses, and they are able to do this efficiently and accurately, and we have had great success using them as our testing model. We have been able to show that the rapid test performance is in accordance with the manufacturer's reported accuracies, and clearly patient satisfaction is high.

So what does this mean for an over-the-counter application? My perspective is, the more barriers you knock down to HIV testing, the sooner we are going to help solve this epidemic. If patients want to be tested in the privacy of their own home, then we should make that available to them. I think it is one potential niche, one particular group of patients, that will take advantage of this test.

Thank you for your time.

DR. DiMICHELE: Thank you very much. I'd like to invite Dr. Richard Rothman to the podium. Mr. James Sykes will be next.

DR. ROTHMAN: Thanks for the opportunity to speak. My name is Rich Rothman. I am an emergency physician that practices clinically in Johns Hopkins Hospital. I'd like to give a little bit of an historical perspective in terms of the need for accessing a population that might not get tested otherwise, and then talk a little bit about our recent experience in pilot testing programs, both in our urgent care center and in our emergency department.

So in terms of need, U.S. emergency departments see over 100 million visits a year. It is a 24-hour seven kind of operation, and it is viewed as a safety net. So in terms of the particular populations we see, we are seeing a

high risk group of patients in terms of those patients being at significant risk for HIV. Lots of minority, under insured, foreign born, substance abusers.

The particular aspects of Hopkins emergency department, although Maryland is 19th in terms of population census with third in AIDS incidence, and Baltimore City has 50 percent of the HIV positive patients, at Hopkins particularly, we are a large inner city emergency department and you can see the distribution of our populations, 15 percent intravenous drug users in our emergency department, lots of unrecognized other infections like STDs.

This is just going to show some quick historical data from Hopkins' experience. There was a doubling of the prevalence of HIV between '88 and '92, and that raise has remained fairly steady for the past ten or so years. We are now at about somewhere between ten and 12 percent of our ED population is HIV positive.

If you look at rates of unrecognized disease reflecting national trends, about a third of those patients have unrecognized disease. So in terms of national perspective, an emergency department use of testing, although from the U.S. Public Health Task Force it was clear about when to recommend testing, the emergency community looked at the evidence for testing in emergency

department settings and reviewed the literature, and the leadership is now recommending routine testing based on high rates of disease throughout the United States in large urban centers. The fact that testing is feasible in a variety of trials, there is high consent rates and high followup rates that parallel that seen in public health settings, and various cost analyses have shown that testing in these settings is equitable to what is seen in publicly funded STD clinics.

In spite of this, around early 2000 several studies looked at what is currently being done, and found that most emergency departments, really the vast majority, weren't offering testing, and most of the issues cited time as the major obstacle.

In terms of developments, the rapid bedside test provided a window of opportunity for testing in this atypical nontraditional setting, with specific issues associated with streamlined counseling that would make testing more feasible in the ED, and offering testing to all patients, like Dr. White was talking about.

Just a little bit of experience from our emergency department. In our urgent care center, this was a provider driven program, lots of different staff members offering testing and providing the test. The particular population here is about 700 patients who were tested.

Many of them had no primary care doc, lots of uninsured. We had about two to three percent prevalence of disease. About 31 percent had never been tested before, so using the rapid test for accessing a population who didn't get tested elsewhere, then in terms of followup, the whole pie makes 100 percent of all the patients who were tested, were plugged into followup. One was a direct referral from the ED and the second 40 percent was with a phone call, a second prompt to get them into care.

Unfortunately, the large majority of these patients who are detected in our ED had late stage disease, highlighting the need for wider and more accessible testing mechanisms.

We have now gone on to develop a program where we are offering testing in our larger emergency department, again, a busier place than our urgent care setting. We did a validation study with the department of pathology and got the OraQuick Advance test approved with the performance characteristics cited previously.

In our early pilot data with the program just starting, we have tested a couple of hundred folks, and we had a four percent positivity rate, and plugged 80 percent of them into care.

So in terms of over-the-counter testing, it is clear that there is a significant disease burden, and you

need innovative approaches in nontraditional sites to access these populations. Our experience with the rapid test is that it is easy to administer. Many different folks were able to efficiently offer the test. It is easy to interpret and it is well accepted by our population.

In terms of challenges and barriers to testing, although it worked in our setting, we believe that offering over-the-counter tests might provide a way to access a population that may not want to get tested in the emergency department, and there are particular issues associated with implementing these testing programs in emergency departments that may make it difficult to make this universal.

Thank you.

DR. DiMICHELE: Thank you very much, Dr. Rothman. I'd like to invite James Sykes to the podium. He will be followed by Mr. Tom Donahue.

MR. SYKES: Distinguished community members, my name is James Sykes. I am representing the AIDS Institute on National Public Policy Organization. By way of disclosure I have not received any financial compensation or have a financial interest in any of the products being discussed, and have not been compensated in any way for my testimony here.

Thank you for considering my public comments

regarding over-the-counter home use HIV test kits. I think it is rather poignant, it is not lost on me that we are having this discussion today, March 10, which is the first annual national women and girls HIV Awareness Days that was organized by the Office of Women's Health at the U.S. Department of Health and Human Services. So this effort is to increase the awareness of the impact of HIV and AIDS among women and girls, particularly women of color and communities of color, specifically African-American and Hispanic women.

With that being said, the Institute supports efforts by the Centers for Disease Control and Prevention and the FDA to increase access to and availability of HIV testing. The goal of HIV testing is twofold, first, that an individual become informed of his or her status so that appropriate medical evaluation and treatment can be sought.

Unlike the early HIV epidemic, today improved treatment options are available to people living with HIV. In many instances, HIV has become a chronic disease.

Second, people who are aware of their HIV status may be less likely to transmit the virus to others. This is an important public health consideration.

The introduction of the HIV rapid test in recent years has expanded HIV testing and increased testing access and availability. One of the advantages of the rapid test

is the relative immediacy of receiving the test result. More conventional testing is hampered by poor client return rates, often resulting in clients not receiving those test results.

The AIDS Institute supports a concept of over-the-counter home use HIV testing kits. Such an approach would further increase access to and availability of HIV testing. This approach can play a role in the overall HIV domestic testing system. In particular the approach may be appealing to individuals who resist seeking HIV testifying in public health settings and private medical practice For these individuals, use of an over-the-counter home use HIV test may be the only approach by which they become aware of their HIV status.

There are a number of issues the AIDS Institute believes must be addressed prior to the implementation of this approach. First, the absence of direct counseling in the over-the-counter home use HIV test kit settings will require the provision of clear information with the kit, including appropriate use of the kit, HIV prevention messages, and a statement that HIV infection is a treatable disease. Secondly, likewise the absence of direct counseling with this message needs to be addressed by the provision of a toll-free 24-hour, seven day a week telephone number staffed by qualified counselors. The

counselors will need to be prepared to answer questions about the test kit and its use, HIV prevention, and local referral options for medical and psychological evaluation and assistance. Lastly, the CDC will need to address how this approach may impact HIV case reporting and HIV surveillance data.

I thank you for the opportunity to present these comments. It is good to be back again. I was here in the fall, and again I think it is poignant that we are having this discussion today, the HIV awareness day for women and girls. Thank you.

DR. DiMICHELE: Thank you, Mr. Sykes. I'd like to invite Mr. Donahue to the podium. He will be followed by Patricia Charache.

MR. DONAHUE: I'd like to take a second and say that I am proud to be the youngest speaker who will be speaking in front of you today. I think what I am about to say is probably one of the most important things, because you are talking about youth, young folks who have the opportunity to take advantage of this over-the-counter HIV test. So it is important that you listen to what I have to say.

Why was I foolish to never think that HIV could infect me? Why is it that I never knew anyone my age that was HIV positive while growing up, at a time when half of

new HIV infections occur among my peers under 25?

There is still so much stereotyping and ignorance surrounding HIV. Because of that, young HIV adults rarely talk about being HIV positive. When no one talks about it, you think it is not there. You think it can't happen to you. I never thought it would happen to me, in a small rural town in Pennsylvania; it did. My actions resulted in me testing positive two and a half years ago, an active, respected young man, a college student struggling to make my way through school, a typical 24-year-old who is like everyone else.

Good morning. My name is Tom Donahue, 26 years old, from State College, Pennsylvania. I return today to this advisory committee to help advise. I am the Executive Director and founder of Who is Positive, a national organization which humanizes HIV to the point it becomes a prevention tool among young adults.

Since my last appearance in front of this committee, I clearly understand the need for you folks to move rapidly forward approving the proposed over-the-counter rapid HIV test. Our organization fully supports the technology of such a great tool in the fight against HIV and AIDS.

Young adults need an alternative. They need to know that they can find out their HIV status without having

to face someone to tell of their mistakes. They need a tool that will give them the information they need while not having to tell anyone other than themselves. This proposed over-the-counter test offers that, a private way to know one's status without having to go to a clinic where a case worker will ask you what naughty things you have done to put yourself at risk, a way that provides support and care while still staying anonymous.

We know that young adults, many young adults, have never been tested, never been challenged to think that they have put themselves at risk. Many see learning about HIV as a task, a requirement that their high school had to explain. So few ever think that they would ever be face to face with HIV.

Society dictates that we only learn what HIV is, not what it looks like, how it acts, whose lives it changes, or how it affects people who are infected or affected. On a college campus such as Penn State University, you have 50,000 students. How many of them have ever thought they could have been exposed to HIV? How many of them look at their crazy nights on the town or their spring break rendezvous as a risk for HIV? Who is opening the eyes of young adults to say, wake up?

Society has yet to deliver a message that says HIV is in your neighborhood; your urgent attention is

needed to help in this epidemic. Place the test in the supermarket. Put a huge sign in the window: Now offering rapid HIV tests. Will this begin to tell society that HIV is important?

In numerous discussions we have had with young adults all over the United States, we found that many times youth want to know their status, but don't want to face a stranger face to face to disclose their mistakes or sexual habits. Many a survey we conducted said that if accurate, they would prefer an over-the-counter test. Some expressed the need to have counseling. Who is positive acknowledges the importance of pre and post counseling. Currently it has been proposed that a 24-hour, seven day a week hotline be made available.

I am going to briefly go off of my written comments and just touch on the counseling and the importance of 24-hour counseling being made available.

First of all, folks, it is anonymous. When I tested positive, I really wanted to reach out to someone. I got informed by my family physician, but I went home. It was about 4:30 in the afternoon, and who was I to talk to after this point? A 24-hour hotline will make the opportunity available for me to reach out any time, for anyone to be able to reach out numerous times.

After four or five o'clock, our work day ends,

but me facing the fact that I was HIV positive continues 24 hours a day, seven days a week. So it is a great opportunity to continue to provide a service to those who may need it at any time. It offers a continual support network.

Students said to us that during the pre and post counseling, many were never truthful on surveys, that in the moment of fear, all they wanted was to get their test and leave. I know; I relate to many of those youth who told me that. I too performed regular routine testing, thank goodness. Otherwise I could be out infecting others right now. I'm not sick, I'm not even on medications, so without regular routine testing I would have no indication that I was tested, no reason to think that for the last two and a half years that I could be infecting others. This mentality is what helps fuel the spread among young adults.

On a campus of 50,000 students, it is estimated that 100 students would be infected. This shocks Penn State students. Maybe it is that popular jock who is unknowingly hooking up with all the pretty vulnerable freshman girls on campus, who are just looking to be popular, who is dying to fit in, to be accepted in the sorority. What a story to tell the sorority sisters who have all been with this jock.

HIV did not only infect me, but it infected so

many people around me. It was one moment of passion, of intimacy, of irresponsibility that changed my life forever. HIV/AIDS is so much more than three letters. Those three letters represent faces and stories, infected and affected by HIV, mothers, fathers, sisters, brothers, nieces, nephews, friends, roommates. Society must wake up and understand they too probably have already been affected by HIV. Some know it, others don't.

Society must open its eyes to an epidemic that stares us in the face every day of every year. Winning this fight against HIV and AIDS cannot and will not be done by keeping our eyes closed. You have a new tool in front of you to help reduce my peers, your sons or daughters or nieces or nephews from being infected. Offer the alternative. Give another option. Continue this fight.

As a growing new nonprofit organization, Orasure Technologies has partnered with Who Is Positive to help in giving us our own tools and helping us get on our feet. Just last week they provided a mobile testing unit from Philadelphia to this very rural community to provide rapid HIV testing. We had well over 150 students show up to be tested, a greater amount that we couldn't even test them all because of it. Additionally, Orasure Technologies has accepted a partnership with its financially supporting an endeavor called Operation Get Tested, where we will take

six HIV positive youths from the East Coast to the West Coast, taking stories and faces of HIV positive youth to schools and universities across the United States. They have also provided my transportation and hotel accommodations for this trip.

With our limited funding, we are proud to once again be requested to make these comments, and I thank the committee, and to continue to provide a youthful perspective on this subject. I would ask that these comments be submitted to the record, and I would be willing to answer any questions that you have at any time. My comments have been typed up and are available outside if you don't have them in your packets.

Thank you.

DR. DiMICHELE: Thank you very much, Mr. Donahue. I'd like to ask Miss Charache to come to the podium, please. You will be followed by Miss Gonzales, Heather Gonzales.

MS. CHARACHE: I will be brief. I have chosen to use a few slides to expedite conveyance of the views of the American Society for Microbiology, who I represent and on whose laboratory practices committee I serve.

These are a summary of the concerns that the next four slides will highlight a few examples of. They are not all of them. I have tried to emphasize those that we

haven't already heard a lot about, but we have heard a lot about the ability of users to correctly perform the test under the range of conditions in which it might be performed.

We mentioned last session the very critical data of the error rate of even wave tests when used in the general population of wave testers, and they showed it to be between 33 and 50 percent of the tests run in physician offices that were wave test offices. We have also seen, of course, as other institutions have -- I am from Johns Hopkins also -- a very unfortunate rise in sentinel events associated with waved glucose testing that had been done inappropriately in the hospital setting, the impact of loss of direct counseling on subsequent clinical and epidemiological followup capacities and documentation of risk of harm data when the test is performed by the untrained, and unobserved public, in the absence of pre and postmarket testing and support controls.

To emphasize the three accuracy considerations here, the home testing can be expected to yield both false positives and false negatives. They can be associated with specimen collection, false negatives with peaking during the 20-minute incubation period, and so on.

We have to consider the low risk as well as the high risk population. Our target is the high risk

population, but in the general over-the-counter usage we can anticipate there will be a lot of worried well from whom the significance of harm from false positives must not be understood, and I'm sure there are many of you here -- I am also an ID consult, and I'm sure many of you have experienced the social and medical harm done with false positives that could not be corrected.

We have heard from Dr. Brandon, an oral test showed a 50 percent positive predictive value rate, and this should be further assessed. I will emphasize, it is very important that we understand predictive values. We can anticipate that the non-high risk users may exceed the high risk users when we consider those who have had a causal sexual experience and a very broad range of others in addition to the usual worried well group.

Under some of the additional safety concerns, we have to emphasize that the direct counseling would not be available to OTC users, and that the documentation on the use of things like telephone inquiries and support as opposed to direct reading support has not been successful in other studies, and this can be confirmed. It may be reasonable to learn how the introduction of such tests affect confirmatory testing and followup care without such counseling, which might be done if one did a pilot in a community that had both high and low risk populations

involved. This might be a good way to do your stage three testing.

The percent of followup patients who return from followup we heard wonderful results on. We support them and we strongly support controlled access to testing, including wave testing, as Dr. Rothman summarized, and almost everyone else here did, but we have to emphasize that wave test results cannot be presumed to correlate with what we can expect from over-the-counter testing.

We know that all the CDC funded studies and many states require additional protections to those required for wave testing that made them safe, and we know that the wave test studies have been done in a setting, including outpatient studies and bathhouse studies in California, where there has been pre and post test counseling which would not directly occur.

Patient harm is clear as I stated before. The false positive results should not be undervalued, and the criteria that is going to be used by the FDA, which is more permissive for OTCs than it is for wave tests or any other tests, and wave tests can be plus or minus 20 percent in accuracy in many instances, that should be known to this body as you make decisions and recommendations for studies.

That is the last slide. So I would emphasize that we favor controlled wave testing and counseling

settings, where we can be far more sure that there will be some type of followup support. I urge great caution with the OTC concept.

DR. DiMICHELE: Thank you very much. I'd like to invite Miss Heather Gonzales to the podium, please. She will be followed by our last speaker, Mr. Corey Dubin.

MS. GONZALES: Good morning. My name is Heather Gonzales, and I am here on behalf of the National Association of Evangelicals. The NAE is a network of churches and ministries from 52 denominations in the United States, and we touch a service constituency of 30 million evangelicals throughout the United States. I'd like to thank you all for giving me the opportunity to speak briefly.

The position of the NAE -- we were here in the fall, and our position remains steadfast on the matter of rapid HIV testing, and the need for such testing to be approved for over-the-counter use. Empowering individuals with the option to take more control over their health care by knowing their HIV status is critical.

To do this, additional testing options such as the availability of an FDA approved over-the-counter oral fluid HIV test which is quick, simple to use and highly accurate is a must. Every day that we delay in making this additional testing option available results in another

potential new infection.

The NAE believes that HIV/AIDS represents one of the most pressing public health concerns of our time, and our position has remained consistent starting in 1988, when evangelicals challenged public health officials to recognize HIV/AIDS as first and foremost a public health concern. The NAE's public comments are backed up by actions and practices. We act and practice. We with compassion offer hope of Christ and His grace to victims of HIV/AIDS, and we cannot permit fear or apathy from bringing life-changing resources of our Christian faith to those who do not know their HIV status and those who suffer from the disease.

Examples of our practice include encouraging our pastors to request that couples who come to them for marriage be tested and share the results with one another. Also, our member churches and ministries have embraced community level programs to minister to HIV victims and their families.

The NAE though also does believe that legislation and the best efforts of public health officials have their limits. That is why we believe our Christian faith offers hope for the victims of disease. Our faith offers a realistic way of life that will help curb the spread of disease by calling for chastity before marriage and

encouraging fidelity within marriage.

Simply stated, the NAE believes it is unconscionable that the number of HIV infections continues to grow. It is time to move the HIV prevention debate from well-intended talking points to clear and present action steps.

As an important action step, the NAE joins with those who call on the FDA to approve rapid oral fluid HIV testing for over-the-counter use. The NAE respectfully requests a copy of these remarks be included in the public record.

Thank you for your attention, and God bless.

MR. JEHN: Thank you. Corey Dubin will be next.

MR. DUBIN: Thank you. My name is Corey Dubin. I am with the Committee of 10,000. We are a national HIV/AIDS advocacy and support agency rooted primarily in the hemophilia and bleeding disorder communities.

In response to the issue of conflicts, the Committee of 10,000 through its bylaws is prevented from accepting any monies or financial support of any kind from the manufacturers of drugs, biologics or medical devices. We do this in part because we believe conflicts of interest so contributed to the AIDS blood epidemic.

I want to focus on the reason we are all supposed to be here today, but a quick background. From 1990 to

1994, I chaired an AIDS consortium in California and then was a founding member and chair of the community planning work group which was California's prevention committee. We think we wrote one of the best plans in the country.

But here is the problem we see. Technology cannot replace good public health work and planning. I think you all have heard a lot of issues at the table that don't relate to the BPAC. As a former member of the committee, I know it is a struggle to sift through a lot of the other things and relate to the meat of the object.

The Committee of 10,000 is pleased at FDA's methodical approach to over-the-counter test kits. We have been concerned about this from the first introduction by Johnson & Johnson. It is not that we are 100 percent opposed to the concept, but the concept in a vacuum we think is very dangerous. As a community that took a huge hit in AIDS, where our agencies and our doctors and the people we looked to for support weren't -- everybody had so much trouble getting their arms around the magnitude of the problem, that we found ourselves frequently in isolation without places to turn. So we understand that.

I am troubled today to hear the argument stood on its head that somehow concern for the mental health and wellness of a client is a financial thing, and muscling a test kit out into the community is the right thing to do.

That for us stands the argument on its head. We believe that concerns raised about counseling are integral to this concept of wellness that we push. Having all gone through this with both HIV and hepatitis-C, I am a 22-year survivor of HIV and close to 30 with hepatitis-C. We figure it is easy to understand that sense of isolation.

I think a lot of what we have heard has really surprised me today. I understand I am a little over the issue, but so is everybody in it relates, so I am going to try to focus it real good. I think it is important to note we are in a climate when Ryan White has had no increased funding in how many years? I think most people know, level funding for five years now. Level funding is not level funding, it is a cut.

We are in a climate with a document that I had thankfully a little piece of drafting, California's prevention plan, also is in tatters, because our governor has chosen not to put the money on the table that needs to be there. So I am a little troubled by all this optimism I am hearing about the changing climate. We think discrimination and stigmatization is still huge issues in this society, and we are concerned about the impact of test kits, and we are concerned about counseling.

We believe that one of the ways to look at counseling is to remove it from the profit stream, remove

it from the stream that generates profits on the kits, set up nonprofit to do it. In California we spent serious time and money training our counselors, and other states did the same. When that training was culturally competent, we had some wonderful successes.

I think this is a climate where those kind of successes aren't going to happen. I'm not suggesting that the people putting the test kit on the table won't attempt to do a good job. I think on their own by themselves, given what they do, it is not the appropriate venue. So I think we have to look at that.

I think where FDA has to exercise a little more control is the phase II and phase III studies. Instead of waiting for the company to come to you with a proposal, I think there are things that FDA could require if you are going to approve this. I think it is incumbent upon you to do so.

This is risky, folks. We have struggled with this issue for many years. I sat at this very table where you sit now, scratching my head, trying to figure out where to go. Our board of directors, mostly people with AIDS, 60 percent of whom have died since that time, struggled with this issue.

So I really appreciate FDA's methodological approach. I appreciate that the BPAC has opened the

hearing and allowed people to speak, but I want to underline something I said a little earlier: Good public health decisions cannot be replaced by technology. Technology has an incredible role to play. In part I stand before you because of recombinant technology in hemophilia got us out of the danger, and we are thankful for that, but it was also mixed with good policy moving towards that at DHHS, at FDA, and we think that is important.

There is one last thing I want to put on the table. We don't live in a society where access to health care is equitable. I have heard too much today that appears to tell me it is equitable. Where is the virus going? It is in poor urban communities, communities of color, poor white communities. I think it is hard to say those communities have immediate access to life saving drugs the way other communities have. We need to consider that.

There is a class issue in medicine, make no mistake. As a person with one of the most expensive diseases, I am well aware of that, because hemophilia has African-American, Asian-American, poor white, middle class white, wealthy white, we have got the gamut in bleeding disorders, so we see how those accessibility questions play out, because our people are tapping ADAP, our people are tapping Ryan White.

So these are critical issues. I know you have to focus on the technical issues. We don't take much difference with the numbers. We think the numbers are good. We think the kits have proven themselves where they have been used in California and elsewhere. That is not our issue.

Again, our issue is counseling, how you do it, what FDA requires of the manufacturer, how you look at the counseling component. Those are the critical issues, because we are making decisions that are going to have extremely long term impact. This disease is loose in the communities we all live in still, and society is turning its back. Certainly the Congress has turned its back. A lot of us are up there fighting this battle. So we don't want something to happen that undercuts it. We would like to see things move in that general way.

Tom Donahue said young people want to see this. I support that. We support that. It is good to see young people at the table. We are very pleased about that. But I think it has got to be done right.

So we want to comment FDA on their methodical nature. We want to urge you to tread lightly with whatever you do, and consider peoples' access to care, public health. We are concerned that the public health structure of this country, which many of us in hemophilia believe in

deeply, is in trouble. So I think we have to consider that when we look at things like home testing.

I would like my remarks submitted into the record, I will get them to you. I appreciate the opportunity to speak to you. It is nice to see the committee. This was a very good part of my life, sitting on this committee. Thank you very much.

DR. DiMICHELE: Thank you, Mr. Dubin. That concludes the public hearing section this morning. I recognize that we are considerably over time. I also recognize that many of the committee members would love to get up and stretch and go to lunch, et cetera, but unfortunately there are some members of this committee who do have to leave early, so with your permission I would like to move on to the open committee discussion and our deliberations before we go to lunch.

Agenda Item: Open Committee Discussion

So with that, I would like Dr. Cowan to please come back to the podium and again go over the questions for the committee which we can deliberate one by one.

By the way, I also want to thank all of the public hearing speakers. You have shed a very important perspective on our deliberations. Thanks.

DR. COWAN: Before I begin the questions to the committee, I just want to mention one more point very

briefly. That is, the discussions and the proposals that FDA is putting forward today are meant to be general for all of industry, and are not geared to any particular company. These could be applied to any company or sponsor who would come to us for an over-the-counter or home use HIV test kit. I thought that should be made clear to everyone.

Questions for the committee. Number one, does the committee concur with FDA's proposed criteria for test performance, analytical and clinical sensitivity and specificity for home use HIV test kits. Can I assume that you would like to handle each of these one at a time rather than go through them all right now?

DR. DiMICHELE: Why don't you go ahead and go through all the questions, and then we will handle them one by one, yes.

DR. COWAN: Sure. Number two, does the committee concur with FDA's proposal for the phase II study. Number three, for phase III studies, which of the options presented does the committee recommend. Question four, does the committee concur with FDA's proposed content for informational materials provided with HIV home use test kits and the steps that should be taken to validate the adequacy of those informational materials to communicate or provide pathways to adequately address issues including

accuracy of testing, correct test interpretation, the importance of supplemental testing for confirmation of positive results, management of psychological and social issues, availability of counseling and medical referral. I should point out, by the way, that in your printed materials E is not included, but we did mean to include availability of counseling in that list as well.

Finally, number five, if the committee does not concur with any of the proposals in questions one through four, what additional information or modification would be needed to support approval of a home use HIV test kit.

DR. DiMICHELE: So open committee discussion on question one, does the committee concur with the FDA's proposed criteria for test performance, analytical and clinical sensitivity and specificity for home use HIV test kits, is now open.

DR. KATZ: The entire discussion this morning has begged the question of who is going to use the kit, because the performance characteristics, the sensitivity and specificity are fairly straightforward, but the predictive value, which is going to be the clinical issue in real use, depends on the prevalence of what we are looking for in the population that is going to use the test.

I have no great feeling for who in fact is going to use this test. If it is a 35-buck that at the Walmart

being paid cash for by the worried well, the risk-benefit calculation is different than if it is a high prevalence population that is currently underserved by counseling and testing services.

I think we have to answer the question of who is going to use it, which I think there is some of in the phase II study. But it is pretty hard for me to answer each of these individual questions without having a better idea of in the real world who is going to access and use this test.

DR. DiMICHELE: So what you are saying is that the answer to phase I in terms of the qualitative research defining the population that is going to use this is of critical value in answering any of the subsequent questions?

DR. KATZ: Yes. I think the numbers for sensitivity and specificity look like they are probably quite reasonable. The FDA hasn't suggested that they have to meet the qualification that the EIAs I use in my blood center do. I think that is appropriate. But if nobody who is infected is going to use it, all the positives are going to be false positives, and we are going to create harm. That is what I can't tell.

DR. DiMICHELE: Good point. Any other comments from the committee members?

DR. DOPPELT: I think it is going to be -- frankly, I think it is a little bit hard to predict really who actually is going to be using it, because it apparently depends upon the cost of the test and where it is going to be available.

For example, for some individuals they may just choose to buy it at Walmart, and in other settings maybe the hospitals or communities will make them available for free, in which case you will be reaching the population that you really want to target. So since we don't know exactly how that is going to play out, I'm not sure that is a reason not to take action on the issue.

DR. DiMICHELE: In other words, you would favor going on with some of the answers to these questions.

DR. DOPPELT: Exactly.

DR. DiMICHELE: Which we could, assuming that access will be uniform and that the distribution of these kits and access to these kits will be available to anybody who needs them.

DR. DOPPELT: My gut feeling is that there is a lot of hospitals that would go out of their way to make it available free. They provide free service under many circumstances. There is a lot of other organizations that would pony up some money to make it available. So I know it is a concern, but I personally think that will all play

out fine at the end of the day.

DR. DiMICHELE: Dr. Kaplan, you can respond, and then Dr. Cryer.

DR. KATZ: It is not just cost. It is how the decision that I need to be tested that I think is as big as cost. I agree with you that my clinic would distribute these things free for people who came in and didn't want to talk to a counselor under appropriate circumstances. I've got a high risk population, there is a yield in that population. The net good that I would do would be just fine.

But that is such a tiny -- the 25 percent of infections that are untested because they don't perceive or in some way never engage with the idea they need testing, that is what I am trying to get my hands around. I'm not saying we should ignore the questions, by the way.

DR. CRYER: I had similar concerns as Dr. Katz originally, but I think Dr. Branson's comment that even though the prevalence determines the positive predictive value, but the number of false positives are going to remain the same. So you precisely know almost how many of those are going to be out there. It just seems to me that as long as we put in proper methodology for dealing with the low number, that we ought to move forward with this.

I think that concern for me has been alleviated

by something I should have figured out on my own, but thanks for pointing it out.

MS. BAKER: I can understand Dr. Katz' concerns, but I have been working with not-for-profit organizations for 30 years -- yes, I am that young -- in the Midwest and the East Coast and the West Coast, with maternal and child health, with unrecognized women's health concerns and with the HIV community as well. I have seen a plethora of not-for-profit organizations, community-based organizations, state health departments working in partnership with the CBOs, some of them represented here. I think that we need to move forward.

I think that I could foresee this as being out in the community, being added to the arsenal of outreach strategies that the injection drug users, homeless youth, adolescents, all kinds of organizations that are currently serving the HIV community would add this and bring this out into those communities and make it available free, using the existing well-trained counselors who have been using this test kit. This would just be another avenue to bring it outside the clinic setting, and you would have all of those well-trained testers being able to in an organized fashion train others, train people in the lay community.

So while we foresee one option of this being at Long's and Walmart's, et cetera, it could also be added to

the very capable wealth of not-for-profit CBOs and state health departments out there that could alleviate some of the fears that we have.

DR. DiMICHELE: Dr. Cohen.

DR. KLEIN: That's Klein.

DR. DiMICHELE: Oh, Klein. I also called you Kaplan, didn't I? Sorry about that. I apologize to both of you.

DR. KLEIN: I also as a scientist share Dr. Katz' concerns, but I think there is no good way to get your hands around this issue today. I think even if you could, it wouldn't predict what next year or two years might bring in terms of the people who would be looking for this test, who would find it available to them regardless of whether it came out as an expensive test tomorrow. So I would be very much opposed to keeping a tool off of the market because you can't define the population that might use it today.

MR. SHARP: I think the bottom line is that once it becomes approved, it is on the open market, and people if they have the money to pay for it they will buy it, and it will get used.

I wanted to just lobby the companies that get approval for this product, that they provide free kits to populations, to clinics, where they can. I think we have

lobbied for that for years with the drug industry, and I think that there should be a mechanism for free kits for this as well.

DR. KATZ: I'll shut up about this after this comment. I am looking for a way to have this. Please don't think that I am opposed to this.

However, I have had a standing offer at my blood center of $500 for the individual that could explain false positive to somebody who hasn't yet graduated from high school and have it understood. It is over ten years, and I've still got my 500 bucks. So that ain't easy, number one.

The harm that we can do for testing a low prevalence population is very significant. I am trying to hear how we get it to the population that needs it, which is a group of individuals who hasn't in any way engaged now. That is why they don't know they are infected. Somebody tell me how we are going to engage a drug user out on the street, trying to score his next fix, in using this test. If somebody has got a program to go out and hand it to him, with this much assurance that it will get used, I think I can figure out a way to be comfortable.

DR. DiMICHELE: Dr. Quinn is going to answer your question.

DR. QUINN: Well, no, I'm not going to answer it.

I'm just going to weigh in here. I thought we were considering question number one right now. I know we are talking about the predictive values and so forth, but the FDA has put out there certain criteria for analytical sensitivity and specificity. The assays we have seen that have been presented are startling in sensitivity and specificity. We don't know what population it is going to get into for the time being, but maybe we will start to address that when we get to questions number two and three when we do phase II and III, am I right?

So right now, we are to vote, or to at least give you feedback, do we agree with your proposed analytical sensitivity and specificity. If that is the question, I just have a followup then. On that, can a manufacturer that is approved clear a way with certain standards of analytical sensitivity and specificity come to you with like the data that we have and say, this is what we have in analytical sensitivity and specificity, is this going to meet your phase I. In other words, they have already been approved, and what they now want to do is shift into phase two and start to see how this is work in practice.

DR. COWAN: Yes, that is exactly correct. Any manufacturer who has an already approved or licensed test will have already met the phase I requirements.

DR. QUINN: Thank you.

DR. DiMICHELE: Thanks for bringing us back to task. I guess Dr. Katz' comments notwithstanding, and understanding that there is going to be some impact on some of the statistics that we discussed, based on who gets it, who uses it, we will proceed with FDA's question number one, that is, do we agree with the criteria for test performance as has been proposed in their proposal.

Does anyone want to begin that discussion? Specifically, one of the questions that has been raised by one of the public forum speakers has been the issue of the potential for shooting too high in terms of the required specificity for untrained users, being a way of maybe railroading test approval in the beginning, in other words, setting our standards too high may prevent the test from getting approved, and have urged us to look at effective sensitivity testing, in terms of getting it out into the population being part of the sensitivity and specificity testing that we should entertain.

So I was just wondering if anybody has any comments on that, would like to weigh in on that question. So is 98, 99 percent positivity, 99 percent specificity for a definition testing and 95 percent specificity for weak reactive positives the goal for this testing. I'm sorry, Elliot, is that not the question?

DR. COWAN: Let me just clarify that. The

proposed performance of the test for clinical sensitivity and sensitivity is 95 percent as the lower bound of the 95 percent confidence interval. The numbers that were being quoted regarding 98 percent versus 95 percent were for some additional studies that will be done with contrived specimens. In other words, the weak reactives would be 95 percent concordant, and the strong positive and the strong negative contrived specimen would be -- the goal is 99 percent concordance.

For the actual read, for the level of agreement between the trained reader and the person interpreting his or her own test would be 95 percent.

DR. DiMICHELE: That is the question.

DR. COWAN: Yes. Actually, I'm sorry, that really is question two, because the numbers that we were just talking about with the contrived specimens fall under phase II.

This does get a little confusing. Number one, what we are addressing is the clinical sensitivity and clinical specificity set at 95 percent as opposed to 98 percent, which is our current criterion for a rapid HIV test. Again, that is the lower bound of the 95 percent confidence interval. So number one is referring to clinical sensitivity and clinical specificity.

DR. DiMICHELE: Which is exactly what you just

explained.

DR. COWAN: Yes. I was just getting away from the contrived specimens.

DR. DiMICHELE: Okay, I think I understand. Does everybody understand? Dr. McGee.

DR. MC GEE: Actually, I'm not sure I understand. Are we talking about measuring in the actual users or as it says here, the professional users?

DR. COWAN: This would be in the hands of the potential users.

DR. MC GEE: So for the potential users you are dropping it below --

DR. COWAN: To 95 percent, that's correct.

DR. DiMICHELE: Given that there doesn't appear to be a lot of discussion about that, is there anybody who has any comments? Because if nobody has any comments, we can go ahead and proceed to a vote on that question. It sounds like we might be ready for a vote.

Vote. Mr. Jehn.

MR. JEHN: Dr. McGee.

DR. MC GEE: Yes.

DR. JEHN: Dr. Szymanski.

DR. SZYMANSKI: Yes.

DR. JEHN: Dr. Quinn.

DR. QUINN: Yes.

DR. JEHN: Dr. Tuazon.

DR. TUAZON: Yes.

DR. JEHN: Dr. Finnegan.

DR. FINNEGAN: Yes.

DR. JEHN: Dr. Cryer.

DR. CRYER: Yes.

DR. JEHN: Dr. Ballow.

DR. BALLOW: Yes.

DR. JEHN: Dr. Kuehnert.

DR. KUEHNERT: Yes.

DR. JEHN: Dr. Manno.

DR. MANNO: Yes.

DR. JEHN: Dr. Quirolo.

DR. QUIROLO: Yes.

DR. JEHN: Dr. Whittaker.

DR. WHITTAKER: Yes.

DR. JEHN: Ms. Baker.

MS. BAKER: Yes.

DR. JEHN: Dr. Davis.

DR. DAVIS: Yes.

DR. JEHN: Dr. Doppelt.

DR. DOPPELT: Yes.

DR. JEHN: Dr. Klein.

DR. KLEIN: Yes.

DR. JEHN: Dr. Brown.

DR. BROWN: Yes.

DR. JEHN: Mr. Sharp.

MR. SHARP: Yes.

DR. JEHN: Dr. DiMichele.

DR. DiMICHELE: Yes.

DR. JEHN: Dr. Katz, do you have a comment?

DR. KATZ: I suppose we will get to my concerns. The answer is yes. I like the numbers.

DR. JEHN: Thank you. All yeses.

DR. DiMICHELE: Great, good job. We are going to move on then to question two. Does the committee concur with FDA's proposal for the phase II study? Elliot, you were wanting us to discuss the proposal in general, is that correct?

DR. COWAN: That is.

DR. DiMICHELE: There are many, many different elements to phase II.

DR. COWAN: There are lots of elements to phase II. Again, these are the observational studies which involve a lot of different pieces.

For the purposes of interpretation of the test, there are three parts. One is self interpretation of the test. The second is interpretation of a contrived specimen, either a weakly reactive, strongly reactive or negative specimen. The third is interpretation of actual

test devices that have examples of all possible test results on them.

DR. DiMICHELE: Comments from the panel on any of the elements?

MS. BAKER: This is the area where the phrase untrained potential users makes me wonder if we should place some parameters that the FDA specifies some parameters of high risk populations for the manufacturers that would propose studies, such as youth, minorities, low education, women, low literacy, sixth to eighth grade.

I know that the FDA has not defined any parameters for the potential users, but I am wondering if we should do so. I think that we should ask the FDA to do so. If the manufacturers come in with no parameters and they are all white male, highly educated, we would have lost a very valuable opportunity for learning some very important things for the high risk populations that are typically not served, and perhaps have the highest need for this rapid test at home.

DR. DiMICHELE: That is an excellent point.

DR. SZYMANSKI: This will be an observational test. If it is observed that the tester makes mistakes, what would happen? Would it cause some change in the instructions or something else? I think that would be the purpose of it, to improve the instruction kit.

DR. DiMICHELE: I'm sure that that would be -- any problems with the performance of the test kit itself or the instructions, et cetera, all of these tests would be done to try to highlight any of this, which I'm sure would then result in changes in the product labeling or in the instructions, et cetera, yes.

DR. SZYMANSKI: Then those changes might increase the sensitivity and sensitivity in the future of the test.

DR. DiMICHELE: So other than defining the at-risk population, does anybody have any other comments on any of the test procedures? Or do you agree with the shell proposal that the FDA has put forth for phase II.

DR. CRYER: I'll just comment. This is the area where there was some request for a drop of the 99 percent to 95 on the interpretation of a spiked specimen. It looks as I read this that it is 95 percent for the positive or for the weakly positive, but it is 99 percent for the negative, and it seems to me that that would be reasonable. If it is blank, it's blank, right? I think 99 percent of the people should be able to figure that out.

DR. DiMICHELE: So what you are saying is, you agree with --

DR. CRYER: I would contend that this as it stands seems to be very reasonable.

DR. DiMICHELE: Very good.

DR. BALLOW: I agree with Miss Baker. I think there ought to be consensus around the table that the FDA ought to define a little bit more about the potential users, because that is going to really bring out the potential problems or issues before going into phase III. I can't vote on this until -- I can't vote in a positive sense until I get more feedback that this is the direction that phase II should go in, to define the population much more clearly, and to make sure that in going into phase II that all these various populations are going to be studied.

DR. KATZ: It may surprise somebody when I tell you I'm not sure phase III is necessary if phase II is done properly. But again, I'm not going to comment on who is going to use the test, because I think you know how I feel.

The other thing that I want to see in here a little bit more explicitly besides how you pick the subjects is how you hand them the test and have them put it in the back window of their car and take it home in July, and on and on. Mainly that reflects concerns that we have heard about heat conditions, but also I think you heard some very cogent information from the American Society for Microbiology about the performance of wave tests in their appropriate point of use. Now we are talking about taking a wave test out of its original point of use into uncontrolled conditions, and I think the population and

that are the two critical issues in these studies.

DR. SZYMANSKI: I just have one question. Namely, where would those sites be for testing, where the testing would be performed, at which sites?

DR. DiMICHELE: I believe that the protocol suggests that these would be geographically diverse sites. Do you want to comment on this, Elliot?

DR. COWAN: We consider it appropriate to do geographically diverse sites, in other words, scattered around the country. Are you asking about the test location?

DR. SZYMANSKI: Location, yes.

DR. COWAN: For phase II that would be up to the sponsor to determine the site, but what we would ask is that the testing venue resemble as closely as possible an actual testing situation.

DR. SZYMANSKI: How can it be?

DR. DiMICHELE: Can you elaborate?

DR. SZYMANSKI: If it is done at home, somebody else is not going to go there with them.

DR. COWAN: Exactly. This would be a situation in which someone would be observed for example through a one-way mirror with a video camera, that sort of thing. So the person who would be observing the testing would be physically removed from the person, in other words, not

just there watching. Granted, it is not an ideal setting, but at the same time it would be one step removed and allow a person to perform the testing in a way that is not interfered with by the tester, by the professional tester.

DR. SZYMANSKI: So it would be in a clinic or something like that?

DR. COWAN: It could be in a clinic setting, it could be in an apartment. It depends how the sponsor would devise the study. We purposely did not put specifications on the venue in which the testing should be done.

MR. SHARP: I have a question about the size of the phase II study, how many participants, do we know?

DR. COWAN: Yes. We are making that a statistical evaluation, so the size of the study should be such that the lower bound of the 95 percent confidence interval would be at least 95 percent.

Depending on how many HIV positive individuals you would identify for sensitivity, that would dictate different sizes of the trial. In other words, it is a statistical evaluation. So rather than say we would like you to do at least 200 or we would like you to do a thousand, we are letting the statistics dictate that and let the sponsor come to us with that proposal.

DR. DiMICHELE: One of the questions I would like to clarify before we move on with the discussion is, you

stated very specifically that these were suggestions, and that certainly the devil is in the details and the specifics would come from the manufacturers who would come forth with their products.

There have been some very specific issues that have been discussed right now around the table, such as what some of the operational stress conditions should be in terms of storage, et cetera, and further defining the at-risk population. Are these some of the specifics that you are looking for from this committee in terms of the approval of the phase II study? Can we add some of these comments, or are we just generally approving the concept that has been put forth?

DR. COWAN: If the committee has any specific issue that FDA should address, in other words, if we should specify to a sponsor that this needs to be part of the study or needs to be part of the system, we would like to hear that.

DR. DiMICHELE: And can those recommendations be a part of the record of this discussion, and they will be taken into consideration?

DR. COWAN: Absolutely.

DR. DiMICHELE: So at this point, we can take for granted that you have heard that defining the at-risk population is an issue of importance, making sure that it

encompasses all genders, ages, ethnic background, socioeconomic strata, et cetera?

DR. COWAN: Yes. In fact, can I just ask a clarification? That is, the first item that we discussed was, were the studies to identify potential users of the test. Our concept of this was that the sponsor was to provide that to us. Am I hearing from the committee that it should be FDA that does those studies, and them makes a determination and directs the sponsors to include in their studies particular groups that have been initially defined, rather than leave it up to the sponsor?

DR. KLEIN: Realizing that all received wisdom doesn't lie either in this committee or in the FDA, I prefer to see a guidance to the people who are going to be submitting their studies, but allowing them to define their studies, since there may be some very smart people in these companies as well.

DR. FINNEGAN: I think the way that you have designed your statistics would suggest that you do need to put some guidance in. If a high number of positive patients within the study population is going to make you spend less dollars on the study, then you just go into a certain part of San Francisco, and you've got your study. That is going to avoid the population that Miss Baker is worried about, and I think she is exactly right. So I

think you do need to provide guidance on that.

DR. DiMICHELE: I have a question actually for Dr. Branson. It involves the design with respect to picking the geographic areas. You did show some very interesting and important data that has also been referred to by Dr. Katz in terms of the positive predictive value of the test relative to the population being tested. Since we are discussing this population being tested, but we are also discussing going to very geographic disparate areas, would the recommendation from the CDC be to still include in terms of phase II testing for this product both high probability and low probability areas of the country?

DR. BRANSON: I think that in the evaluation of the test kits themselves for professional use, the requirements from the FDA should probably be similar here, in that you evaluate them in high risk and low risk populations, in high prevalence and low prevalence settings.

In some of the data that we showed, you test high risk people like STD clinic attendees in a low prevalence setting like Phoenix, and then you test high risk people in Los Angeles in a high prevalence setting like the gay and lesbian centers. I think that is what we are talking about.

If I can go back to Elliot's slides, this was a

concern we discussed a little bit before. We do want the manufacturers to identify who they think will be potential users of the test, but in the second bullet it said clinical trials should be done in these identified potential users. I hear the committee saying we would like clinical trials to be done in some other populations that might not be identified as potential users by the manufacturer's study. Is that what I think I am hearing the committee saying?

That was my theory. You would go to a mall and do some intercepts and say we think all these middle class people who shop at White Flint are going to be potential users, and I would not want to do all the studies in that population.

DR. DiMICHELE: I don't think that is exactly what is being said here. I think what is being suggested -- and please, anybody who is making these suggestions, correct me if I'm wrong -- that there be some attempt by the FDA to define or help define the at-risk population and not just leave it to the manufacturers. What we have heard here is that there should also be a lot of give and take and potential for everybody to weigh in on this issue.

DR. BRANSON: Yes, I think we want a heterogeneous population. I think it should be the way the FDA does it for the regular approvals, in terms of taking

into consideration potential users and levels of risk and levels of prevalence, the same way they do for the original approvals of the tests.

DR. KATZ: Being simplistic perhaps, but there are 25 percent of HIV infections that are apparently undiagnosed in the country. I am very, very interested in accessing that group, and i am finding it very, very hard to figure out the performance characteristics of the test in that group, and also the implications if it is a $35 test that you buy over the counter, so that the worried well are going to buy it, then the risk-benefit related to false positives.

So I want this test, but I am very troubled by who is going to buy it, or who is going to access it.

DR. BRANSON: Was that a question?

DR. KATZ: Yes.

DR. BRANSON: From the perspective of CDC, we do not see the over-the-counter test being the solution to the HIV epidemic. We have several strategies, including expanded testing in medical care settings and expanded testing in non-clinical settings, targeting people at risk, which we think will do a substantial amount to address, the 25 percent of people who don't know that they are HIV infected.

However, our experience with the home sample

collection kit was that many people purchased it who had never been tested before, and we anticipate that may happen in this case. We anticipate that what the clinics call frequent flyers may end up purchasing this test kit in order to continue monitoring themselves over time. There is benefit in knowing that you are negative as well as positive.

So I think this may supplement the other activities that will help to identify these uninfected people, but our experience from the home sample collection kit is that a diverse group of people are going to buy this, some of whom have been tested before, some of whom never have. I don't think that we are going to be able to answer your question until it is out on the market.

DR. DiMICHELE: Are there any further comments before we go up for a vote on question two, which is, does the committee concur with the FDA's proposal for the phase II study?

What I would like to do is, I would like to go around and actually have a vote on this issue. If there are comments that people want to add to their vote that they feel are very important for the FDA to consider, please add them as you go around the table and vote for whether we should proceed with phase II or not. Is that acceptable to the committee?

DR. JEHN: Dr. Szymanski.

DR. SZYMANSKI: Yes, I agree with that. I would have liked to see the pamphlet that is going to be given to the people, to be able to evaluate it more thoroughly.

DR. JEHN: Dr. Quinn.

DR. QUINN: Yes, with the caveat that the FDA provide guidance to the populations that will be enrolled into the phase II, specifically what Miss Baker has alluded to, as well as what Dr. Branson has said, high risk and low prevalence, low risk and high prevalence, et cetera. I think they do need the guidance, but I think they will know how to find the populations once they have that guidance, because they are used to doing these studies.

DR. JEHN: Dr. Tuazon.

DR. TUAZON: I agree, with the same comment about the at-risk population.

DR. JEHN: Dr. Finnegan.

DR. FINNEGAN: Yes, with Miss Baker's suggestion.

DR. JEHN: Dr. Cryer.

DR. CRYER: Yes, with the same qualification.

DR. JEHN: Dr. Ballow.

DR. BALLOW: Qualified yes, with the comments that were made before.

DR. JEHN: Dr. Kuehnert.

DR. KUEHNERT: Yes.

DR. JEHN: Dr. Manno.

DR. MANNO: Yes. We had hoped that maybe with some excellent phase II results to obviate the need for a phase III. So I think that might deserve a little more discussion.

DR. DiMICHELE: In terms of going on to phase III?

DR. MANNO: One of the options for number three is to consider no phase III studies, as I recall.

DR. DiMICHELE: Right, and we are going to have a discussion of that.

DR. MANNO: Dr. Katz had mentioned that with excellent phase II studies complete, we might get all the information we need to obviate the need for phase III studies, which would delay licensure and be very costly.

DR. DiMICHELE: And we will have another discussion of question three to follow this one, but thank you.

DR. JEHN: Dr. Quirolo.

DR. QUIROLO: Yes, with the same caveat as the other members. Maybe implied in that is the fact that low income people and people with lower education also be included within that group. I hope that the FDA would set guidelines for those people as well.

DR. JEHN: Dr. Whittaker.

DR. WHITTAKER: Yes.

DR. JEHN: Miss Baker.

MS. BAKER: Yes, and I would like to add consideration of one non-English language used in some of these tests.

DR. JEHN: Dr. Davis.

DR. DAVIS: Yes.

DR. JEHN: Dr. Doppelt.

DR. DOPPELT: Yes, and I would just add that I think the reading level eighth grade is perhaps a little bit high. It might be more like fifth grade.

DR. JEHN: Dr. Klein.

DR. KLEIN: Yes.

DR. JEHN: Dr. Brown.

DR. BROWN: Yes, with a couple of concerns that may apply to phase III more than phase II. But I think that probably phase II should be weighted in terms of patient selection more toward the scientific question that is trying to be answered rather than some of the social concerns about different groups that are being raised. I think they can perhaps be best addressed in phase III in terms of the kinds of patients that will be studied.

Also, I think phase II, even though it is not said, it is implied that there will be some kind of clear informed consent that the patients would sign. I bring

that up because it seems to me, in listening to some of the emergency room talks, in which I have a lot of current experience on acute hospital wards and acute emergency rooms, that one of the concerns is that often patients really don't understand what they are buying, or if they were to be buying something outside of a hospital or even in the hospital, they don't understand recommendations. Often when the patient is not nearly at the level of there being a legal criteria for any kind of involuntary decision about health care providers, all you are left with sometimes is giving the patient an informed consent, saying you know you can come back 24 hours a day, here is a list of doctors, if you feel suicidal. This is for all kinds of high risk behaviors, not just the issue of HIV.

So I think it is going to be very important that the patients at least give an indication that they understand what they are doing. I think that certainly would be implicit in phase II. I'm not sure it is implicit in phase III though, from what I read.

So that is a long yes, but those are some concerns.

DR. JEHN: Mr. Sharp.

MR. SHARP: I'm glad you brought that up. I was thinking the same thing about the informed consent process for the phase II studies.

I also wanted to add the laundry list of populations of IV drug users. I don't know if anybody mentioned that or not.

DR. JEHN: Dr. DiMichele.

DR. DiMICHELE: Yes. In addition, I agree with all the comments that were made around the table. I also would like to address the issue -- I think that the companies putting forth their proposal for phase II studies ought to also include in their phase II studies proposals for plans for integration of this test into existing public health structures, and also some proposals for where the gaps are with respect to access to this test, and begin to understand and maybe put forth some proposals as to how these tests would allow greater accessibility, and where public health access needs to be changed to take full advantage of this test.

MR. JEHN: Dr. Katz, do you have anything else to add?

DR. KATZ: Well, the population issue with FDA and CDC participating, and with the manufacturers defining who to test, I think is big.

Just another reminder to really stress the process of using the kits in a very real world scenario, because those of us in clinical settings that understand that wave tests performed in physician office labs, which

ought to be a pretty good place to use them, are used improperly all the time. So I have that concern about this.

The other is that the counseling bar need not be so high as to be unachievable. The quality of counseling that goes on in many venues now isn't really all that good. I think one of the presenters mentioned that.

DR. JEHN: Those are unanimous yeses. All qualify.

DR. COWAN: If I could just add that it is FDA's intent to require informed consent for the phase II studies. Sorry if that wasn't mentioned before.

DR. JEHN: I think it was clear in the materials that you submitted.

DR. DiMICHELE: We are going to proceed to question number three. For phase III studies, which of the options presented does the committee recommend? Does the committee want a review of the three options that were presented by the FDA, or do you feel like you can go ahead and discuss them?

DR. COWAN: I can summarize them very briefly.

DR. DiMICHELE: Okay, go ahead.

DR. COWAN: Option one is full-blown clinical studies to evaluate both the sensitivity and sensitivity of the test in the hands of the potential users, as well as

the ability of the informational materials to substitute for live counseling, to address the laundry list of issues that we have listed.

Option two is to say that the sensitivity and sensitivity as determined in the phase II studies is sufficient to transfer into the real world setting, and that the purpose of the phase III studies would then be just to evaluate the ability of the informational materials to substitute for live counseling.

Option three is the easiest, which is no phase III. In other words, phase II will adequately address all of the concerns, and that a study in the real world setting would not be necessary, would be redundant.

DR. DiMICHELE: Thank you.

DR. KLEIN: I don't see why these options have to be exclusive. It just seems to me that so much depends on the design of the phase II study which we are going to, as always, allow the company to propose. If you said that there were these options available, depending upon the design of the study and upon the results of the study, because of course these are looked at by, I presume, data safety and monitoring committees partway through, then one could eliminate a phase III altogether if you had an appropriate phase II. Or for someone who didn't want to spend all that money with the possibility of not getting to

market, a more limited phase II would result in a full phase III.

So I guess what I'm saying is, I don't want to select number one, number two or number three, but give people the option of doing that.

DR. KUEHNERT: I just had a question for clarification, and a comment. The question is where postmarketing data would fall into this. A lot of this discussion, we know who the intended users should be and who we want to be tested, but then there are the actual users, and we don't know what the balance is going to be between those two. You really are only going to figure that out when the test is out there.

So I am just wondering where we can weigh in on that, and where data should be collected -- where we think data should be collected in the postmarketing arena.

DR. DiMICHELE: Do you want to answer that, Elliot?

DR. KUEHNERT: There is no option for that, so I just wonder where would that best go of the options.

DR. COWAN: It would really default to the public health system. It would be awfully difficult, we think, to require a sponsor to do the postmarketing studies, because of the enormity of the situation. This is a test that would be in the hands of people, and it would be difficult

to understand who has the test at any given time. It could be purchased, for example, over the Internet, in a store, in a whole variety of different ways. So it would require partnership with federal agencies, it would require partnership with community-based organizations and local health agencies, state health agencies.

I know it was an omission from our proposal, but that recognizes the complexity of that situation. We are not minimizing the importance of postmarketing studies. The logistics are daunting.

DR. KUEHNERT: But would there be any role for a company in that sort of a situation that would be required, or at least strongly suggested?

DR. EPSTEIN: We struggled a lot with this, because there is an appeal to saying you are not really going to know what is happening until the product is being commercialized, can't you monitor the outcome. The problem is that the company no longer knows who has the test and what they did with the result.

So the users of the test either will or won't end up in the medical system, and the best followup would be from sites that do confirmatory testing and counseling and care. It is conceivable that public health systems or CDC could set up some kind of outcome monitoring based on determining how do people get their test, what brought them

into that setting. But to expect that the company would somehow sponsor that seems just a little bit difficult. It is hard to imagine how that would actually work.

DR. DiMICHELE: Dr. Branson, did you want to make a comment, since you stood up? I know there was an issue of public health agencies weighing in on this.

DR. BRANSON: I think this is a similar circumstance that we encountered with the home sample collection kit. As Matt points out, you don't really know who is going to use it until you figure out who buys it. I think it would be appropriate for FDA to encourage the manufacturer to work with the public health system, because it would make it easier for me if they would put a coupon in the test kit saying call this number after you use the test so I could measure it. So I would like to see that be encouraged, but I'm not sure we can place a requirement on the manufacturer, because it is going to be a pretty big undertaking.

DR. CRYER: It seems to me that -- I agree with Dr. Klein. If the company put the elements of option two on the phase III trial into their phase II trial, then they probably wouldn't need a phase III trial. But if they didn't, then they would have to do option two at least, in my opinion.

DR. BALLOW: I was actually leaning towards only

option two, but then when you think about the third phase as close to real life as possible, though it is still not what is going to happen when it gets out there in the general public, but it is at least a lot closer than the second phase.

The issue has been brought up about what the environment can -- what impact that may have on the kit, for example, storage in the car or heat sensitivity, et cetera. That may change false negatives and false positives. So now I'm thinking there is no way not to do option one, because it is as close to real life as possible, and there may be factors that are unanticipated during phase II that may come up in phase III when individuals are using this in an unsupervised approach.

MR. SHARP: I'm not necessarily concerned where this happens, but I would really like to see where you have an option two, determining the effectiveness of the materials and how they are being interpreted and used, and how they work out. So I don't know where that would fit in, but I think that is important in some phase of the research.

I think it is crucial to have community input into the design of the materials. I don't know exactly how that would fit into an FDA requirement or not, but I think Dr. Wong in his public comment mentioned focus groups. But

if it is not a focus group, some sort of process which we have done many times before, that can look and see what these materials are doing and if they are actually worded correctly, language appropriate and so forth.

DR. COWAN: That could actually be done at the level of the company. So for example, a company could engage the services of a community-based organization and say is this working for you, and it would help that that would be the case.

MR. SHARP: And that is how it is done, but is there any teeth behind that? Is that a regulation?

DR. COWAN: Not a regulation. It is up to the company to decide how to do that. But it is something that we could encourage.

DR. FINNEGAN: A question for the FDA. What I heard this morning is that technologically this test is really good, but it is very operator sensitive, if you like. Of the false positives that we saw, they were done in the hands of people who had been trained, and perhaps there were some environmental stresses placed on the materials. But it was either an operator or an environment, because there were loci, if you like.

So my biggest concern is not that this test doesn't work. My biggest concern is putting it into the hands of people who are A, a little bit concerned and B,

not very well educated, is going to end up with problems.

So I think option two -- my question is, can you do this in a focused postmarket survey? In other words, could they pick certain groups that they worked with before that they could follow up on this, so that you are not delaying getting it to market.

But this is going to be the biggest problem. This is where either there is going to be trouble or things are going to flow. So that is my biggest concern.

DR. DAVIS: I don't really know which option to choose for question three without knowing the results of a phase II study. I don't know what kind of problems will be encountered in a phase II, and it is hard to address how to troubleshoot that without knowing the results.

DR. DiMICHELE: One of the things that we are being asked to do is to anticipate what the potential limitations of a phase II trial might be, and what the anticipated requirements of phase III might be, understanding that the potential for phase II to answer all the questions is there, but maybe not realistically.

DR. DAVIS: There are often unintended consequences that come up that we may not even think of here today.

DR. COWAN: Just to clarify, I want to make sure people understand -- I think you do, but I need to say it,

anyway -- the inherent difference between phase II and phase III.

Phase II are observed studies. So people are coming in, they know they are being watched, or they think they are being watched, and maybe acting in a certain way. Phase III on the other hand is a case in which it is completely up to the individual to do the test when he or she wants, where he or she wants, and how he or she wants. There is much less control. Phase III replicates the real world setting -- has the potential to replicate the real world setting much more than a phase II study would.

I just wanted to make sure that that was clear, the distinction between the two types of studies.

DR. KLEIN: I just wanted to get back to Dr. Finnegan's point, because I think it is an important one. I don't want to over interpret the data that you presented. I don't think it is necessarily either environment or operator, because there is a certain biology here.

Certainly we who have -- Dr. Katz is not here -- tested blood over the years with the EIAs have found that occasionally at a certain time of the year you get a lot of false positives. Maybe it is the flu and maybe it is the flu shot, and maybe just manufacturer's test kit. So that may be biology and not operator.

DR. DiMICHELE: I also would just like to say

that one of the major advantages of this test that we have heard over and over again today has been the fact that a rapid test would get people to do the confirmatory testing, to seek counseling much more effectively than conventional testing would be.

Certainly I don't see anything -- in the phase II design I'm not sure that we are going to be able to test that. I think the only way we are going to be able to test that is in the phase III trial design and in some postmarketing surveillance, as Dr. Kuehnert has suggested, in terms of how are people using this, what are the true false positive and false negative rates, and most importantly, when people are taking this home and they are not sitting in a clinic face to face with somebody who is doing the rapid phase testing, is it going to allow them to access conventional testing and the counseling and everything that we want them to do any more effectively than conventional testing has. I don't think that phase II has the potential to help us understand that point.

So we either have to do this as part of phase III studies or in postmarketing surveillance. Postmarketing surveillance is going to be difficult to do, and I think we have a role for phase III studies.

Dr. Branson, did you want to make a comment to that? Why don't you do that, and then Dr. Cryer and Dr.

Szymanski. I also want to tell the committee, we have a bit of a problem. If we don't break apparently at 1:30, we are not going to be able to have lunch here in the hotel. You guys have been so patient, and I'm sure that having no lunch is not an option. I also don't want to shortchange the discussion, however.

One of the things that we can do is finish with our comment period and maybe vote on three, and then come back and have a vote on four, if anybody feels this is necessary. I would have liked to have finished everything before lunch, but I'm not sure that we are going to get a chance to do that and still have all the discussion.

With that, Dr. Cryer.

DR. CRYER: I just would respectfully disagree a little bit with what you said. While I think a phase III would be a wonderful thing to do, I just think how to do it. If you let the guy take the kit away and then you somehow have to measure all of these things, I'm just at a loss as to how to do that, that would really give you any more information than a phase II.

The only way you are going to assure that you get the information you want is to give them their 20 bucks when they call you back, and that is not a lot different than knowing you are being watched. I have a little trouble figuring out how to do that. It would have to be

expensive and take a long time.

DR. SZYMANSKI: I think that at the time when a person buys the kit, maybe somebody could do this right and give a number to that person, and then see if the results are conformant between these two tests. It might be unrealistic, but I think that might be one way of doing it.

DR. DiMICHELE: I do believe that in the study design there was supposed to be some methodology for reference testing as well in both phase II and phase III, so I think that is written into the study design. Was there another comment?

DR. DOPPELT: As I was listening to that last comment, I think doing the phase III as I think about it is more complicated than I originally thought. If the question for example is, are they going to get counseling, perhaps they will call the line, maybe they will go to their local hospital or their physician or something. So how much information you are actually going to get back may be negligible. So I'm not quite sure.

It is a good idea to do if you were assured that you could get the information back. Not knowing that, I'm not quite sure how you would implement it effectively.

DR. SZYMANSKI: The only reason you may be able to get the information is when you are doing the HIV reporting. Maybe you have another checkoff list that says

how you do the over-the-counter test instead of the World Bank or EIA. I guess that is one way of recovery of information. But I don't know how accurate that would be in terms of numbers.

DR. DiMICHELE: Are there any more comments from the committee, or are we ready to vote on question three?

DR. QUINN: I'll just throw this out. In some studies we have talked about doing phase IIA or IIB, IIB being a much more powered study, larger numbers, diverse populations. It brings in all the things we have been talking about. If that IIB also brought in option two from the phase III in terms of how good was the proper use of the test and the limitations and so forth, that would be another way that, if the manufacturer came forward with a IIB, would that satisfy some of these criteria.

I know it is not one of your options here, but it seems like the committee is going back and forth over this, between a IIB and a III.

DR. EPSTEIN: FDA has also appreciated that the design of phase III studies would be difficult. On the other hand, we have had a few ideas about how one might go about it. For example, you could have very limited marketing, in a test area, and for the comment to the phase III trial, at the time that the test subject acquires the product they would consent to have followup; by taking this

product you are entering a study and what you are agreeing to is that we are going to be able to recontact you.

It is at that recontacting that you can then do all the things you want to do to validate the result. You can do the cognitive evaluation, you can get a followup test, it can be an OraQuick test or other rapid test. It could be a blood test. So you would get the test validation as well as the cognitive evaluation.

Dr. Szymanski has suggested another alternative. I don't think you could do the oral fluid test at the time of acquiring the test, because then you would have modeled how to do it for the test subject. On the other hand, you could acquire fingerstick blood and then say what you are agreeing to is that we are not going to give you results pending your communicating back to us how you did with the oral fluid test. So that is another possible design.

So we do think that designs are possible. What we are really asking the committee is, how compelling is the case that you should do a field study where people without any prompting and without their process being observed, take the product to wherever they want to do, do it however they are going to do it, and then you try to get some followup assessment of right and wrong answers and comprehension and care seeking.

So we think it is not inconceivable. Our

thinking is that what you learn in that kind of field design is different than what you are going to learn in the phase II design, and there is no amount of pushing the phase II design that gets you quite to what you might learn in phase III. The bugbear is that phase III will be difficult.

So that is the kernel of it, how compelling is it. We could simply take the position, we will cross that bridge when we come to it. We have this concept within FDA of end of phase II meeting, and then you make a decision of whether to proceed to phase III. We can structure it that way. The problem that I see with the logic there is that there is a presumption that tests that do badly in phase II aren't going to go anywhere.

So I think the committee should be thinking that for products that do really well in phase II, then what? Are you done or are you not done? I think that is the way the issue has to be framed, is the value of the information from a study in a much more field environment so compelling that you think you can't get it out of phase II, and you ought to try really hard to come up with some sort of protocol.

It is never going to be an easy one. That won't be an easy study. It will be costly, it will take awhile. But we do think there are feasible designs, and we have

tried not to prejudge those designs, for all the reasons that Dr. Klein said. There are lots of clever people out there, and they come up with very interesting ways to do this that we haven't thought of.

DR. DiMICHELE: I think we might go ahead and unless anybody has any other comments, let's go ahead to a vote on whether phase III studies should be done and if so, among the options presented, which one would you espouse. If you have any other statement, this is a qualitative vote, so if you have any other statement you can make that, too.

DR. JEHN: Dr. Szymanski.

DR. SZYMANSKI: I don't know, really. I abstain.

DR. JEHN: Dr. Quinn.

DR. QUINN: My perspective on this is that because trying to get this type of information that we are all talking about in a postmarketing survey is non-existent and is not going to work, I'm going to vote yes for a phase III. So that leaves two options, either option one or two, because option three was no phase III.

So I do want diversity. When I read one, I see it has got to be three different geographical areas, different populations. I like that still, as well as what is listed in option two, not the word limiting, but at least going into the informational materials and how well

is the counseling going.

So I guess right now I am going to lean towards the option one, a little more rigorous. I am saying that because there is no way once it is licensed for OTC you are going to get that kind of information. This is your one chance to collect that.

DR. JEHN: Dr. Tuazon.

DR. TUAZON: I would offer option three, but with the caveat that depending on the results of phase II studies that we will need the phase III studies.

DR. JEHN: Dr. Finnegan.

DR. FINNEGAN: I vote yes for phase III and I challenge the FDA to come up with some options between one and two.

DR. JEHN: Dr. Cryer.

DR. CRYER: I would vote yes for phase III unless the information in phase II is compelling.

DR. JEHN: Dr. Ballow.

DR. BALLOW: I vote for phase III with option one for the reasons I said before. This is as close as you are going to get to real life conditions, and you are never going to be able to go back to determine whether the overall objective by providing a valid test is really going to come true, unless you look at option one.

DR. JEHN: Dr. Kuehnert.

DR. KUEHNERT: Why do I feel like i am answering a K type multiple choice question? I would say option one, given that we don't know what the results of the phase II studies are. But I would say that option two might be acceptable. It really depends on the design and the results of the phase II studies and also, and I know this is going to be really hard to gauge, but the commitment of the company to work with public health on postmarketing evaluations.

DR. JEHN: So that is a yes with option one?

DR. KUEHNERT: Yes, with option one.

DR. JEHN: Dr. Manno.

DR. MANNO: I vote yes with option two. I am very interested in hearing the results of the phase II studies. That is my caveat.

DR. JEHN: Dr. Quirolo.

DR. QUIROLO: I vote yes for option one.

DR. JEHN: Dr. Whittaker.

DR. WHITTAKER: I vote yes for option two, and also the phase II studies are very important.

DR. JEHN: Miss Baker.

MS. BAKER: Yes for option one for the same reasons mentioned by some of my colleagues.

DR. JEHN: Dr. Davis.

DR. DAVIS: I vote yes for option two. I think

option one is going to be very difficult to accomplish. There are a lot of people that really don't trust the federal government when it comes to studies, especially some of the diverse populations we are talking about. I think it is really going to be difficult to get people to -- especially with strings attached, getting the information from them.

DR. JEHN: Dr. Doppelt.

DR. DOPPELT: I would vote yes for phase III, option one. I think taking Dr. Epstein's comments, I'm not quite sure how you would do it effectively, but forgetting about the details of how you are going to do it, in principle will you get valuable information. I think no matter how good phase II is, phase III is asking a slightly different question, and it isn't going to give you the information unless you do the phase III, option one.

DR. JEHN: Dr. Klein.

DR. KLEIN: I would still like to give the company the ability to design the phase II trial, whether you call it a phase IIA and B or phase II/III study, which some people have called it, I don't know. I guess what I am saying is, I don't think that necessarily a phase III would be required if the phase II were appropriate.

Let me say parenthetically that phase III studies, although considered the gold standard, can give

you the wrong answer if you don't do it properly. It is not necessarily going to give you the right answer. This is going to be a tough one to design.

DR. JEHN: So you would like to say no?

DR. KLEIN: If the answer is whether you need a phase III, I am going to give you a not necessarily.

DR. JEHN: Dr. Brown.

DR. BROWN: I'm going to vote to do phase III, option one. I think that one of the additional valuable issues that the companies have to look at, everybody talks about the value of counseling, but very little has been said here about how it is going to be done, as well as the patients to whom I was referring previously. There are going to be a lot of patients who are going to be offered something that probably won't do anything. I think it will get more of the data on how to handle those kinds of questions from phase III than we are from the more rigorous, scientifically controlled phase I and II.

DR. JEHN: Mr. Sharp.

MR. SHARP: Okay, now I'm really confused. I really like the IIA/IIB design concept. I would vote for somewhere evaluative data on the materials and the counseling components somewhere built in, whether it be a phase IIB or a phase III.

DR. JEHN: Dr. DiMichele.

DR. DiMICHELE: I would vote yes for phase III and for option one, just because I don't believe that there is any way for a well-designed phase II study with all of the goals of the phase II study to really encompass a lot of what can be learned from phase III.

I agree with Dr. Ballow. I think it is one chance to go ahead and do it. If it can be done reasonably with a reasonable study design, I think it should be.

DR. JEHN: Fifteen yeses and one not necessarily.

DR. DiMICHELE: Before we break, does anybody feel -- for the record, could you read those people who voted for option one versus option two?

DR. JEHN: Yes. Dr. Quinn, option one. Dr. Tuazon, option three. Dr. Finnegan, one and a half. Dr. Cryer, one. Dr. Ballow was one. Dr. Kuehnert, one. Manno, two. Quirolo, one. Whittaker, two. Baker, one. Davis, two. Doppelt, one. Dr. Klein was the not necessarily. Dr. Brown, option one. Mr. Sharp was two. Dr. DiMichele was one.

DR. COWAN: After we break for lunch, if we could possibly get a tabulation it would help us of how many voted for which option.

DR. JEHN: Yes.

DR. COWAN: Thanks.

DR. DiMICHELE: Does everybody feel like there is

going to need to be some discussion of question four? I'm seeing some nods. Question four, does the committee concur with the FDA's proposed content needed for informational materials provided with the home use HIV test kits, and the steps that should be taken to validate the adequacy of the informational materials to communicate or provide pathways to adequately address issues, including adequacy of testing, correct test interpretation, correctness of interpretation, the importance of supplemental testing, management of psychological and social issues, availability of counseling and medical referral.

PARTICIPANT: Looks good.

DR. DiMICHELE: Looks good? Okay. if the FDA is okay with this, I think we will go straight to a vote on this, because it doesn't seem like there needs to be much discussion. Once again, let's go for a vote, and anybody who has any comments can go ahead and state them in the vote, just so we can get this done.

DR. JEHN: Dr. Szymanski.

DR. SZYMANSKI: Yes.

DR. JEHN: Dr. Quinn.

DR. QUINN: Yes.

DR. JEHN: Dr. Tuazon, yes. Dr. Finnegan.

DR. FINNEGAN: Yes.

DR. JEHN: Dr. Cryer.

DR. CRYER: Yes.

DR. JEHN: Dr. Ballow.

DR. BALLOW: Yes.

DR. JEHN: Dr. Kuehnert. He is absent. Dr. Manno.

DR. MANNO: Yes.

DR. JEHN: Dr. Quirolo.

DR. QUIROLO: Yes.

DR. JEHN: Dr. Whittaker.

DR. WHITTAKER: Yes.

DR. JEHN: Miss Baker.

MS. BAKER: Yes.

DR. JEHN: Dr. Davis.

DR. DAVIS: Yes.

DR. JEHN: Dr. Doppelt.

DR. DOPPELT: Yes.

DR. JEHN: Dr. Klein.

DR. KLEIN: Yes.

DR. JEHN: Dr. Brown.

DR. BROWN: Yes.

DR. JEHN: Mr. Sharp.

MR. SHARP: Yes, just with the addition of medical and non-medical referrals.

DR. JEHN: Dr. DiMichele.

DR. DiMICHELE: Yes.

DR. JEHN: Sixteen yeas.

DR. DiMICHELE: And that I think obviates the discussion for question five. Does the FDA need any more information from us, or should we break?

DR. COWAN: I believe we can break. I want to thank the committee, or FDA would like to thank the committee for all of the input. This was precisely the type of discussion we wanted to have and the input we wanted to receive. So a heartfelt thanks to all of you.

DR. DiMICHELE: And my thanks to all of you as well.

(The meeting recessed for lunch at 1:45 p.m., to reconvene at 2:27 p.m.)

A F T E R N O O N S E S S I O N (2:27 p.m.)

Agenda Item: Summary of the Office of Blood Research and Review Site Visit

DR. ALLEN: The afternoon is going to be spent discussing two site visit reports. Does anybody have any objection if we reverse the order and go with the review of the research program site visit for the Division of Hematology Laboratories first? I apologize for the sudden decision, but it is absolutely essential that we have the subcommittee chair here for that discussion.

What I would ask of Dr. Golding and your staff, is that we have extremely brief presentations that are to the point. I think everybody has had a chance to read the background materials and the background report. So let's move on with that and then get on to the discussions. But if we could keep the presentations very, very short and succinct, that would be extremely helpful with the process. Dr. Carbone, you are the first, and then Dr. Epstein, and then we move on. Were you going to do an overall review or just for the OBRR site visit?

DR. CARBONE: I was just going to give an overall CBER research, and then I think Dr. Epstein was going to do OBRR overall.

DR. ALLEN: Why don't we go ahead and do that? That will be fine. We will save the discussion on the OBRR

report until after we have done the other one. So let's go ahead with the presentations.

DR. CARBONE: We talked to our staff and we are committed to trying to be brief, so we will do our best. We know it has been a long day.

I apologize that my talk you didn't receive in your packet. It will be e-mailed to you for your information.

The first slide is the new mission that we are working on developed by Dr. Goodman at CBER. I think the important change here, and this is also a change you see in the FDA mission, is the goal to facilitate. The way Dr. Goodman has often explained this is, better, safer products faster. So that is what we try to do with the research program.

This is briefly the work chart. I just wanted to point out that we have three offices that do standards of research approaches, Office of Vaccines, Office of Blood and Office of Cell Tissue and Gene Therapy, and here today we are to consider the Office of Blood.

What is the challenge? When the critical path paper was released from the FDA, some people commented that the $800 million figure for development of a drug to licensure was too high, except subsequently, a science publication came out suggesting that it was really closer

to two billion. This is not a cheap process. The cost of this and the delays of developing drugs obviously limits the number of good quality medicines that can be out there. These are problems that we have to address.

In many cases, CBER products are products either without a regulatory pathway or with very complicated and indefinite regulatory pathways that need definition, and the pathway has to be made clearer. That is where the role of research can help speed the process.

So in asking for the office site visits, as with the individual lab site visits, our goal was to get help from the committee in ways to better improve and meet this goal.

There is an issue with science and the concept of management of science. In the article in Science magazine, individuals from Wyeth and from Genentech were both quoted on the concept of managing research and the oxymoron of managing a very creative process. But yet, if we are going to intelligently seek to identify, focus on and solve challenges in the regulatory pathway, there clearly is a need to manage the research process. On the other hand, in order to make some resolutions, we need to maintain creativity, and that makes the issue of how to manage the creative process a very difficult one, but something we are working on.

The critical path process is defined starting very early. We are not in the basic research or discovery end of things necessarily, but when a prototype is discovered, the earlier we intervene or get involved in the process, the better. CBER has always had a tradition of pre-IND and pre-pre-IND meetings and pre-phase III clinical trial meetings, and these are all designed to prevent problems coming at the end. The concept is, failure is good if you fail here. Failure is not good if you fail here. It is expensive and it is a drain on resources.

The critical path initiative at the FDA also makes clear that research is not a little adjunct activity off on the side, but is actually part of the process. Dr. von Eschenbach has said over and over again that the regulation should be a science-led regulation. Science is there to inform the policy. Policy may sometimes have to precede the science or even sometimes lags behind, but at least it has to be informed, because uninformed policy is always worse than informed policy.

What are our guiding principles in research, and how do we make sure that this program has added value? The research program will be highly collaborative and include all kinds of research. When we say research, we don't limit it to the laboratory. The scope will encompass all the scientific basis of preclinical and clinical studies,

manufacturing which is often overlooked in the greater population and outside industry, and the science of review, regulatory submissions, postmarketing surveillance and the use of that science in creating guidances.

In order to expend the meager resources we have on research, we have to make sure that we use new high quality resources done efficiently, directed and managed to provide outcomes that are very important and directly address gaps in the knowledge and scientific tools that we need to regulate out complex products.

Why CBER? Why does the FDA get involved? There is a unique role of CBER in the research mission. That is, in general the innovators, discovery if you will, they create scientific tools, but they create them typically for their individual product, and that information often remains proprietary.

CBER research regulators on the other hand are people in a sense like sponsors that are experts in both product development and a scientific discipline, and as such, that unique expertise can be applied, but more importantly can be applied and provide information in the public domain.

Because we see successes, failures and missed opportunities across whole classes of complex biologics, we can apply this information in a general form to help move

whole entire classes of products ahead, and by identifying where the gaps are, the misunderstandings and the problems, we can provide a clearer, more predictive regulatory path. Even we can play a direct convening and coordinating role of scientific needs across sponsors.

Sometimes eyebrows get raised when we talk about competing sponsors collaborating to get scientific questions answered that are holding up product development, but in fact, the FDA has served that role. There was an example with computer software to evaluate digital mammography, and no single sponsor had enough samples to get significant information about the value of their software, but they agreed to pool all these data in a blinded fashion, and were all able to draw from that pool of data and were able to get their products approved.

Multitasking. As with academic where I came from, our staff need to be good multitaskers in order to survive as research regulators. They are fully integrated into the regulatory process, which is fairly unusual in the FDA. Most research groups in the FDA serve as consultants, but our people are the people sitting on committees with their regulatory scientists, clinical review, et cetera, and statistical colleagues. They do everything for standard review practice, including inspections. But importantly, they take that information from sitting on a

committee and work with their managers to develop plans to do actual research and to be the people who solve some of these problems.

How can we actually work? Do we do all the research in the world ourselves? No. What we want is the best information possible. So what we try to target for intramural programs is work that is not being done elsewhere, that is not recognized elsewhere, and fill in these gaps where our expertise or our recognition of a problem is not being seen or addressed in the regular community. When we find individuals that complement our talents or are adding to our research programs, of course we do that collaboratively, but as importantly, to be able to raise the issue of a critical path type research for the extramural world, and to encourage others to go independently and work in these important questions is also the goal of the critical path program.

So all these sources are used to contribute to the decisions that we make, and no holds are barred in terms of finding the correct information.

One concept I have tried to move forward is the concept of, NIH does basic and you do applied research. In fact, that is simply not true. The type of research is not the issue, it is the question that it answers that is the issue. So no matter what we do, whether it is in basic

biomedical discovery or developing an assay, it is how it is applied to the regulatory pathway that is important, and both have been done at CBER, and both have made huge strides internationally in moving products forward.

I gave two brief examples from blood. One is very basic, redox and adverse events information that has come from the HBOC group, very basic biochemistry, and yet is critical in identifying adverse events, and perhaps for methods of inhibiting them, and then you have straightforward methods validation for inactivation of TSE. That has also been done. So we can cover the gamut. But the key is, what is the applied value, applicable value.

We collect research reporting information and identify literally hundreds of biologic licensing applications and investigational New Drug Applications that are directly supported by research programs. I am leaving it to staff from OBRR and the leadership to provide information. But a review of the program shows that an emphasis in CBER is product safety, followed by quality, efficacy and other. I think the product safety emphasis is because those are often the stickiest questions. For example, safety typically, not efficacy, drives the size of a clinical study. So the more we can do in preclinical testing or understanding the safety issues better, the more efficiently we can regulate.

What is the major focus? Creating efficient, high quality regulatory pathways where there are none, applying 21st century science to improve the efficiency and accuracy of established pathways. We must constantly be moving forward, because it is not GMP, it is CGMP, so current state of the art must always be considered in applying to regulatory pathways.

We focus on outcomes, identifying and resolving specific high priority scientific challenges and product evaluation. Data quality is critical. OMB has a new initiative on peer review of data, and so this is why publication of the information, presentation of data to advisory committees such as yours, and external site visits are critical to get information on the quality of our data and the focus of our program.

Increasing CBER research impact is high on our list. It is difficult. As I have said many times, what is the first question I get out FDA research? It is, oh, you guys do research? The second question always is, why do you guys do research? So we clearly need to do better in that arena.

I have one individual helping me, for example, with some of our web-based management. That poor individual has been under a lot of pressure lately, and finally has succeeded. By the end of the month the

external website for CBER research, which will list the virtual teams of scientific expertise and individual programs with summaries and publications will be available on the CBER website by the end of the month. We have many other initiatives ongoing, but that is obviously one big one.

We had the good fortune of having several of our programs listed in the NIH Catalyst, which was the successes in NIH intramural programs, and they kindly included our research in their listing. We have tried to increase the number of workshops that we hold, both in regulatory training and also on the research impact. Media representation is very important. I think a constant -- my going around trying to advocate for the research is finding important meetings on important products that list every government agency except the FDA. So I also urge the public and the members of the committee to keep their eyes open, when they think the FDA should be involved in a meeting, please let us know, and we will do our best to get there.

Funding the efforts. Obviously once we have a quality product we need to get it funded, and then providing core research support. I think again, having come from academia, one small light in the darkness is the fact that we have a very good molecular core support and

animal facility support, beyond what I ever saw as an academic, and I think they take good advantage of that.

Just to finish quickly, how do we manage these? In all the offices there is a process for determining priorities. What we are working on now is making a consistent across-center process that we go through. It is quite complicated, and I don't have time to list it. But because research is the Titanic, we have to basically prepare five years ahead at least for issues we might be facing. As a result we have to be very good with the crystal ball. We have to be prepared to deal with immediate crises, we have to be prepared to deal with products that may not be high in the public issues but they are coming, so we have to regulate them properly. There are just a multitude. I hope at some time in the near future, hopefully within the next 12 months, to be able to present to the committee our specific paradigm that we have adopted across the Center.

Internal and external evaluation of past research achievements like this are currently being performed. We have talked about the outcomes, and we have talked a little bit about the internal reviews and the external site visits, which are all very critical. Quite expensive, but with our meager resources we continue to invest in external reviews, because it is just absolutely critical for us

doing a better job every time.

The Research Leadership Council has been formed, composed of central leadership. OBRR has representation in both the research leadership and the regulatory review leadership. Those are the three goals we have set. We want to develop cross-cutting research priorities and communication strategies for our relatively small research populations. It is imperative we do the best communicating across the Center that we can. Then we have begun to develop Center-wide matrix programs where appropriate, and we call those virtual teams. That would be the scientific expertise that is represented in the office, bring them together so that we have greater critical mass. The groups are generally organized in product offices, so the product expertise is currently clustered, but we want to cluster as well the intellectual scientific area expertise, and that is in the works.

I will just finish with some examples of critical path investment opportunities. We welcome obviously all the suggestions either in the report or outside the report. Generally better characterization of self therapies and blood products, linking this characterization to clinical outcomes, appropriate toxicology approaches for complex biological products, new assays, standards, biomarkers and surrogates for efficacy and quality, multi-path and rapid

detection methodologies, methods and validation of pathogen inactivation, improving longevity, storage of cells and tissues and enhanced clinical trial design analysis. Dr. Goodman has charged me with developing a workshop to talk about pathogen detection and inactivation broadly across CBER products, and more on that hopefully to follow.

I just wanted to finish with, thank you very much for your time and effort. I know it has been a long day. I'll finish up there.

DR. ALLEN: Thank you, Dr. Carbone. We will come back and ask questions. Dr. Epstein.

DR. EPSTEIN: Thank you very much. In this next segment you will be engaged in the overview of the site visit, which was the first of the kind of CBER. It was an opportunity for you to review the research in the office as a whole as opposed to the laboratory programs in specific.

I won't repeat the very nice summary that Kathy just gave you on CBER's vision. What you are going to be hearing hopefully is how the Office of Blood Research and Review operates to fulfill this very vision.

First of all, who are we, what do we do. This office is the primary FDA component responsible for facilitating development, approval and access to safe and effective blood products. In particular, our scientific functions are related to regulation of blood derived and

analogous products, let's say recombinant proteins, for example, all the medical devices that are used to test, collect, to process or to store donated blood, and a very major program there is the infectious disease screening test and the blood group compatibility test, and also because of an agreement reached with our sister Center for Devices and Radiological Health, we regulate all the retroviral diagnostics, but we also regulate HIV and AIDS related tests.

Our structure is as shown here. If you look at the bottom of the slide, we have three divisions, Emerging and Transfusion Transmitted Diseases under Dr. Nakhasi who is here and Deputy Paul Meade, and then the Division of Hematology, you are going to be hearing some lab site visit reports from that division, director, Dr. Golding, and we have recently hired Deputy Director Susan Abondanzo, and then the Division of Blood Applications that I don't think is represented here today, Dr. Ellen Williams is the director and Sharon Orten is the deputy. My immediate staff, I have a deputy director. I have a couple of positions in transition, associate directors, and a small policy staff, also in transition.

The main thing you need to know is, two of the divisions are laboratory based, that is the Division of Emerging and Transfusion Transmitted Diseases and Division

of Hematology. Research also goes on in the Division of Blood Applications, but it is mainly epidemiological or methodological research as opposed to wet labs.

Our responsibilities are divided in these divisions. The Division of Blood Applications looks at the blood and plasma licenses, blood establishment software and blood grouping and HLA reagents. They also provide the administrative center for managing our review process, which you probably know is under user fees for the pharmaceuticals and also the devices, though not for the blood components.

Within the Division of Emerging and Transfusion Transmitted Diseases, the chief concerns are the blood donor screening tests for infectious disease, retroviral diagnostics, but we also have a small program related to certain vaccine development because of the expertise of those individuals. Then in the Division of Hematology, they have the responsibility for the bacterial detection devices used in the platelets, for all the plasma derived programs, all the derivatives including IgIV albumin coagulation products, alpha 1PI, et cetera, for the blood and blood component collection devices, including the containers and the aphoresis machines and also for the hemoglobin based oxygen carrying solutions and plasma expanders.

I won't dwell on this. This is essentially the same slide set I showed to the site visit team in January of 2005, except that I have added a few updates. This is our regulatory workload in 2004. Not to dwell on the numbers so much as the fact that we deal with every regulatory category that exists in the Food and Drug Administration. That cannot be said for other working components of the FDA. We deal with all the device categories as well as the NDA drug categories, as well as the biologic license applications and supplements. This represents a very, very large workload in terms of person hours.

These were the figures for 2004. The figures for 2005 are a little lower, in that we have had fewer submissions. But there are certain critical differences. For example you will notice here, we have 18 biologic license applications compared to 15, well, an addition of three; one biologics application might equal a half a dozen supplements, so this is still a very, very large workload.

Let me just give you some of the highlights to orient you toward our work products. In late '04 and through '05, and the committee members will be familiar with this, those of you who have been in service more than a year, we have brought forward rapid tests for HIV-1 and 2 on oral fluid, novel barcode scanner for matching the unit

to the recipient, and now we have approved several such systems, stand-alone computer-assisted interview systems, software review, new immunohematology, anti-RHD and IgIV products, the first NAT test for hepatitis-B virus, the mini-pool test was approved as a voluntary additional screen to HB SAG, tests for bacterial contamination for quality control, and use in conjunction with certain collection containers as a release test, novel tests for anti-core with better specificity. The West Nile virus, we licensed the first one for donor screening. We have approved platelet pooling and storage containers as the first pre-storage pooling system in the United States, a new hepatitis-B immune globulin, making the marketplace more robust, and the first immune globulin for subcutaneous use, which creates options for patient convenience and may have some theoretical benefits also for efficacy.

In the area of guidance and rulemaking, we have a barcode rule which contained requirements for machine-readable code for blood components. The draft uniform history questionnaire is a significant advancement in validation of donor questioning as well as standardization across the industry. We have issued a final guidance which established through reference to regulations a requirement for the implementation of nucleic acid tests for HIV-1 and hepatitis-C virus. We published a draft guidance on the

evaluation of hemoglobin-based oxygen carriers, setting for the development plan, guidance on implementation of West Nile guidance screening. Yesterday we discussed the guidance on automated platelet collection, which is a whole series of new safety and program standards. Updates on the collection of disease associated source plasma, a guidance on clinical trials of immune globulin intravenous in primary immune deficiency, which has greatly simplified the ability to bring forward new products based on much smaller clinical trials modeled against historic controls.

We have held workshops. We had a workshop on plasma freezing to try to understand how the conditions of freezing and storage might relate to the quality of the end products, of Factor 8 in particular. A workshop on platelet standards and novel approaches to assessment of modified platelet products. A workshop on the efficacy and safety approach to immune globulins, trying to look at surrogate markers, for example, for new products. We cosponsored meetings with the SOLGOT. That is an international body that develops standards for gene amplification technology. We cosponsored last year's meeting of the IPFA and Paul Ehrlich Institute NAT workshop, which actually is a very broad-based review of transfusion transmitted infectious disease. We held a workshop on strategies for development of rare plasma

proteins for rare disorders, a workshop on leukocyte reduction, updating the recent scientific information.

Additionally, we have been innovative internally. We are very mindful of our need to develop high quality work on time, compliant with the user fee programs. We have instituted office level standard operating procedures for various types of review like the 5-10-K and biologics license application and supplement, also standards for approaching the industry meetings, things like how we approach minutes, pre-meeting materials. We have developed review checklists.

Sorry. Do you want me to just stop?

DR. ALLEN: We have to get done in a few minutes and wrap up.

DR. EPSTEIN: When?

DR. ALLEN: We are losing our chair in ten minutes.

DR. EPSTEIN: In ten minutes? So we could I suppose cycle back. Let me just hit the high points.

Anyway, why do we do research? I think that Kathy Carbone has already established that we have unique roles to play as FDA. We have been doing this for a long time. There have been research contributions to product advancement and safety for decades, running easily back to the 1950s with our antecedent organization.

You have my handout, so I'll skip over the examples of research accomplishments. These are important, and I do hope that you will read them.

Dr. Carbone has already explained to you the general paradigm under which we engage in our laboratory activity as part of what we now call the critical path for medical product development. I'll just spend the next minute or two giving you some examples of how critical path works.

So for example, in the blood safety area there is a need for new technologies to screen blood donors for a large number of pathogens simultaneously. Our actions have been to develop prototypes of a multiplex NAT test, DNA microarrays, and more recently working on nano technology. Additionally, we have provided FDA reference panels. The outcomes have been the identification of the critical path parameters for assay development, standard panels that can be targets for industry. This has the effect of reducing the industry investment and cost. Here is some of the output. This is a microarray. What it shows you -- you're not going to be able to read it from where you sit, but it can simultaneously detect and confirm all the major transfusion transmitted viruses as well as potential buyer terror agents and also bacteria.

Another example. This is the approach to

counterterrorism, a major activity for us. Smallpox vaccination if we ever need it can cause life-threatening complications in immunodeficient individuals and those with atopic allergy and eczema. The efficacy of a vaccine immune globulin as a treatment for these complications could not be tested in humans because we are not vaccinating against smallpox, so our laboratories developed a SKD mouse model to test the efficacy of vaccinia immune globulin both as a prophylactic and a therapeutic. The outcome was that these methodologies were transferred to the industry. The model was incorporated. It became a pathway for licensure, and on this basis we were able to approve the vaccinia immune globulin intravenous based on the animal efficacy rule.

This just shows you the results, how you can improve survival if you prophylax with the vig IV. There is another model for therapy.

Then one last example, a critical path related to hemoglobin based oxygen carriers. The problem is that blood availability for trauma victims in rural areas and in disaster situations including war is very constrained. The early generation of hemoglobin based oxygen carrier solutions were extraordinarily toxic, vasoconstriction, high blood pressure, multiple organ damage.

Our laboratories developed a program in which

they determined the linkage between the oxidative chemistry of a given hemoglobin and its toxicity. They developed an in vitro and an in vivo model to better understand the toxicities of blood substitutes. The outcome is that preclinical testing is becoming more predictive, and that a second generation of hemoglobin-based substitutes is now in development and was facilitated by this research.

I'll skip over new candidate alternatives.

So the conclusions are -- and I hope we convinced the site visit committee -- that research is critical to the OBRR mission, that mission related research facilitates product development on the model of the critical path, that our research program is indeed focused on regulatory concerns related to product safety and efficacy, that it includes the prevention and control of blood-borne infections, characterization and standardization of blood products, and methodologies for product review and surveillance.

Thank you very much for your overview of our July site visit. I cede the podium to Dr. Goldman.

DR. GOLDMAN: I am the division director of the Division of Hematology. As you know, two of the laboratories were site visited.

This is the structure of the Division of Hematology. There are five branches. All of the branches

perform research except for the clinical review branch, but the clinical review branch is involved in doing research related to adverse events, so they have access to the adverse event reporting and have published some papers. The other branches do bench research. You see in the bottom panel the number of principal investigators in each branch. There is a total of 11.

The site visits that we are talking about today refer to the Laboratory of Biochemistry and Vascular Biology and the Laboratory of Cellular Hematology. I'll skip over the mission, because this is clear to you by now.

In terms of the scope of regulation and research in the division, the research helps to solve regulatory problems, critical path, serves to enhance the expertise of scientific investigators who have review responsibility for these products, and are involved in the scientific evaluation of biological products derived from blood, which include those isolated from blood or plasma, and analogous materials derived from by recombinant DNA technology.

The clinical applications are diverse, and you can just read through the list very quickly. But the point that I would like to make is that because the scope is so huge in terms of the clinical applications. We do need the clinical expertise to review these submissions, as well as the research divisions to look into the mechanisms of

adverse events and safety of the products.

Regarding the regulatory products and process, I am going to skip this slide and I am going to talk about the research topics.

The research topics relate very clearly to the products that we regulate. The research topics include coagulation, immunology, protein structure and function, blood-borne viruses and TRC prions, oxygen carrying compounds and platelet structure and function.

The personnel actions that we are asking for this committee to look at relate to the conversion of Andrew Shrake from a GS-14 to 15. He is actually retired, so this is somewhat academic. We are also looking at the biochemistry section, the Laboratory of Biochemistry and Vascular Biology, for the progress report for Dr. Abdu Alayash, who heads this branch and is also the section head. Also, he is a staff fellow. Yiping Jia is a candidate for conversion to a staff scientist, and we are asking for his progress report to be approved.

In the vascular biology section we have Felice D'Agnillo, and we are asking for his conversion from a visiting scientist to a senior investigator, which implies a permanent position.

In the group of the Laboratory of Cellular Hematology, we are asking for the conversion of Yarasow

Vostov, who heads that branch, from a GS-14 to 15, and a major investigator in his group, Jan Simak, is going to be reviewed, and we are asking for a progress report.

So because of the time constraints, I have just got a few minutes. I will just highlight some of the research that I am not going to have a chance to present to the committee, so I just want to mention some of the accomplishments of the group.

Dr. Alayash has involved in the hemoglobin substitutes, and Dr. Epstein pointed out that his group has unraveled at a chemical level the abnormalities in some of the earlier hemoglobins. This has led to a much clearer understanding of how these products should be manufactured to avoid the toxic effects. In terms of Dr. Felice D'Agnillo's research, he has developed an endothelial system in vitro to look at toxicity of hemoglobin substitutes, and he is also working in the counterterrorism arena, looking at anthrax and looking at the toxic effects on endothelial cells. In terms of Dr. Vostov's branch, he himself was involved in developing a model in mice to look at platelet survival so that the implication is that that model could be used to test platelet survival instead of in human studies. This is work in progress. He also works on prion diseases. Dr. Simak is our nano technology expert, and he has been studying microparticles and looking at

microparticles in different blood products, and correlating that with possible adverse events of those products. Dr. Shrake who is retired was going to be represented today by Ewa Marszai. The two of them, Dr. Shrake and Dr. Marshall, have done studies on alpha 1PI on the polymerization of alpha 1PI, have published their findings in the Journal of Biological Chemistry. Their model was based on data was accepted as one of the likely models to explain how alpha 1PI polymerizes. This is very important in the Z mutant disease because it is associated with sclerosis and understanding the underlying biochemistry, may lead to treatments to avoid the polymerization in the sclerosis.

Have I left out anybody? I don't think so, so I'm not in trouble. Thank you very much.

DR. ALLEN: Thank you, Dr. Golding, and thanks to all of the FDA staff for your succinct presentations and cooperating with an abbreviated schedule here.

Let me take just a minute and ask, does anybody on the committee have clarifying questions for Dr. Carbone, Dr. Epstein or Dr. Golding while we are in open session? No questions?

We will at this point clear the room and go into closed session for discussion of the draft reports.

(Whereupon, the open session was adjourned at 3:05 p.m.)