My concern is we are just jumping from one unvalidated to another unvalidated, and I don't think that is the way to go. I think we really should encourage the appropriate tests to be done to validate the actual questionnaire.

DR. EPSTEIN: I just wanted to add a few historical notes, because I sense the general frustration why hasn't this field moved faster. Just a few perspectives, first, that the FDA twice funded studies on the use of direct oral questions for high-risk screening. This was a study done by the American Institute for Research. It is the Donna Mayo study that was published.

It was FDA dollars that funded it, and at that point in time, which was early 1990s, around 1990 or so, the issue was introduced in questions for heterosexual risk, and questions that had been studied--I draw a little bit shy using the word validated, but at least studied--were then proposed in FDA guidance.

Now, FDA never said that the questions had to be adopted verbatim. Indeed, in all FDA guidances, we say that alternative validated methods are acceptable, but I think what everybody realizes is that validating questions is a very

expensive proposition, and so there hasn't been a lot of that done.

Later in time, toward the end of the '90s, we became very concerned about supply issues, particularly in the wake of introducing the deferrals for classic CJD and then vCJD, and so with the increased concern on supply, one of our initiatives, again government led, was to try to remove barriers to safe donation, and one of the elements of that initiative was the recognition that we deferred a lot of donors because of questionnaires without knowing that these were validated deferrals.

But once again, it was recognized that true outcome measures, which is what you are talking about, were difficult to obtain, that you would like to be able to show differences in marker rates between donors who did and did not defer, and ultimately, you would like to know about impacts on residual risk because, after all, even if you had differences in marker rates, you remove the marker positives, it is the marker false negatives that you are worried about.

But once again, those are very expensive propositions. Short of that, the FDA solicited an

industry-led initiative on the Uniform Donor History Questionnaire, and we have been highly cooperative with that initiative, but it has been focused more at sort of the normative level of, you know, do donors comprehend.

We think that that is a step forward although we all recognize that it is short of any ultimate validation in terms of safety outcomes.

So, this is where we are. I guess I am trying to say all this to sort of disabuse the notion that the problem has been that the FDA has been ignoring this. We recognize that use of questionnaires has come into play, you know, dating back to the 1950s without formal validation.

We can only be where we are, and I think that these are steps forward, and I would note also that the NHLBI did fund the first development of the computer-assisted interview and that implementation of it was studied in a second study with America's Institute for Research, which was the second Donna Mayo paper cited.

So, you know, we have been trying to be proactive, but there simply have been limitations which are technological. I mean these are difficult methodologies and economic. These are

costly studies and sources of funding have not materialized.

DR. ALLEN: Just a comment and one quick question. I think this historical perspective is important and, Jay, I appreciate what you just said. Certainly early in the AIDS epidemic, there were regular conference calls involving the blood collection centers, the FDA, the CDC, and others, and as it became apparent that questions were not doing the adequate job of having people self-defer who should, the questions were changed.

The most obvious one in 1985 was the change from asking people or telling people if they were homosexual, they should not donate without asking the question directly to using the concept of behavior, men who have sex with men.

I think there is still a lot of refinement in some of those questions now that has got to be looked at very carefully. I mean in particular asking people have any of your partners ever had that. I suspect most people have no idea.

I am not sure that the blood-collection centers--certainly the FDA has done some work in the past. CDC has done a little bit. The NIH has some done. This may be an area where we need to

put out a very strong call for additional resources.

Putting this advisory committee together on safety and adequacy has some recognition of the level of the problem, but I am not sure this translated into appropriate resources, and that probably is something that ought to be addressed at some point.

My question really is with regard to the comprehension, the general comprehension questions. I assume that if somebody indicates that they have got a question or didn't understand something fully, there are notations made on the donor collection form.

Do you have any idea about the frequency with which that was done or what the type of response was?

DR. PAGE: You are correct that in the Remarks sections of the blood donation record, it is noted if there were any questions of that nature, and the answers may be changed. I don't know the frequency, but we can retrospectively review for that.

DR. NELSON: Thank you.

Celso, did you want to--I erroneously

attributed Mary Townsend to American's Blood Center.

DR. BIANCO: It was not your error, it was maybe our error.

I am Celso Bianco. I am with America's Blood Centers. That is an association of 75 blood centers. They are community based and collect about half of the U.S. blood supply.

We were active participants in the AABB Task Force and donor history. We support entirely the conclusions of the Task Force including the self-administered questionnaire. I would like to reemphasize what has been said by many here. This is new. That is, even with limited funding, limited resources, we are able at least to address issues of comprehension, to address questions that are so complex, so crazy, that really lead to a lot of confusion on the part of the donors.

I would like also to remind the committee the words of Dr. Boyle, that the questionnaire is not a test and that no matter how perfect we try to be with the questionnaire, we are not going to get 100 percent sensitivity and 100 percent specificity or 99 percent specificity that we get with our tests.

It is one of the layers of safety that we have, and with sufficient information, we can address and actually improve, as Dr. Epstein presented, the deferral rates for inappropriate reasons.

One final point that I want to make very quickly, I want to give Dr. Williams a slightly different interpretation about post-donation information. Post-donation information, all donors are offered the opportunity to call the blood center back and say, oh, I realize that a question that I answered to this morning or yesterday or two days ago was not the correct answer. I told you that I had not been in a malarial area in the past year, but actually, I went home, I looked at my passport, and it was 10 months ago, and the blood center will attempt to retrieve these units or most often, because of the short time, is able to retrieve those units, but will report to FDA as post-donation information, and this goes to the deviation reports for which Dr. Williams indicated that the most frequent or among the most frequent issues are travel questions.

Second, are at risk behavior questions. I consider that a success of the current lousy

medical history that we have. These people went home thinking about those questions. They asked their girlfriend or their boyfriend, they went to look at a passport, they checked their travel history, and they realized that they said something that was not accurate, and they went to the trouble of picking up a telephone and calling the blood center to say, look, what I told you is not correct.

Donors are very concerned. They don't want to hurt patients, they want to help patients, and most often when we get inaccurate information, obviously, there are all the behavior issues that were raised here, but particularly travel questions, they are not embarrassing questions, they relate very much to lack of information, confusion about dates, the temporal relationship of things, the confusion that in the way we currently ask the questions, that we will ask something that happened last week, three months ago, a year ago, all mixed up, and then we ask even a question is you had sex with another man since 1977, when most of us cannot, at least the older ones like me, cannot remember what we were doing in 1977.

The actual question that we should be

asking is behavior in the past three, four weeks.

So, just to finalize, I want to emphasize that our enthusiasm for the new proposed Donor History Questionnaire, the improvement that this represent for the life of blood donors and for the life of blood centers, and hope that this whole discussion will stimulate more funding and more studies for a true validated questionnaire.

Thank you.

DR. NELSON: Thank you.

MS. CIARALDI: Dr. Nelson, my name is Judy Ciaraldi. I am from the FDA. I wanted to give an update on the review of the new questionnaire that was part of your handout, the proposed questionnaire from AABB.

There was a comment that we hadn't communicated our findings yet. The evaluation of AABB's proposed questionnaire was discussed at the last BPAC, the June BPAC, and we discussed what our preliminary findings were from nine out of the 10 reviewers, four of which were BPAC members.

We also mentioned that we were going to review this with an internal group and come out with a written response to the Task Force. We have just finished that review, and we are now preparing

our response.

Thank you.

DR. NELSON: Thank you.

There is one other person, Paul Cumming wanted to testify or make a statement. Is he here? I wonder if you would be as brief as possible because we have to then discuss the questions that were posed to us, particularly if areas have been covered by other speakers.

DR. CUMMING: I will do my best. I have very hard to get the presentation down to 10 minutes or less. I have taken out a lot of the pretty graphics unfortunately.

[Slide.]

What we have provided was a summary of the literature on alternative methods of donor interviewing, which we provided to the committee in advance. By "we," I mean myself and Louis M. Katz, a physician from the Mississippi Valley Regional Blood Center.

[Slide.]

It needs to be noted upfront that Talisman, the company I am with, produces the Quality Donor System or QDS, an audio-video touch screen computer-assisted self-interviewing system

or AVT-CASI as opposed to A-CASI which you have heard about.

[Slide.]

We undertook the task of looking through the literature because when we read the AABB's Streamlining Task Force and the CBER draft guidance materials, we noted a distinct lag or aging to the literature on computers and what they were doing.

I forgot to mention we are partially supported by the National Heart, Lung, and Blood Institute with grants. For those of you who are familiar with the grant process, that means we have to submit what we propose to do and the credentials of our people in advance and get the pass-through peer review before we can even do anything, and then we publish everything we can.

This was also what was referred to earlier as a priority of the Department of Health and Human Services and their Five Point Plan, which is on the blood safety and availability web site.

The literature that we reviewed, we went online, did easy stuff basically, shows that audio-CASI technologies to be superior to paper and face-to-face interviewing with regard to literacy, truthfulness on socially and legally sensitive

questions, clarity, donor satisfaction, and likelihood of return, as well as error reduction.

[Slide.]

Literacy arises as an issue because printed and electronic questionnaires presume donor literacy and illiteracy is a large and often hidden problem in the U.S. According to the Census, at least 21 million people speak English less than very well.

[Slide.]

Health illiteracy has become something which has been increasingly recognized. The American Medical Association has a page on their web site which, among other things, notes that nearly half of all Americans may struggle with understanding basic health care information.

Sixty-seven percent, two-thirds of patients with read difficulties are successful in hiding it from their wives.

[Slide.]

This is literature or points from the American Medical Association web site, and I was just noting one of theirs being how much the problem is hidden from even spouses.

[Slide.]

If two out of three health illiterates hide the deficiency from spouses, how do blood center staff detect it? Further, doesn't it make more sense to use technology to prevent or minimize reading problems?

[Slide.]

On blood donor illiteracy, there is no direct data. There is a study, however, of health literacy among 1,000 Baltimore residents by a gentleman named Al-Tayyib, who is a member of the Turner Group, some of the data which was shown before.

It showed that 18 percent of subjects with some college or a two-year degree were reading at the levels of eighth grade or below. This "some college" group is sometimes cited as typical of blood donors.

The group went on to point out that this provides important evidence of the potential benefits of audio-assisted self-interviewing technologies.

An update to that, the AABB presentation listed a study by Wu of 900,000 first-time donors. That study set out that 64 percent of them had less than a college education and 12 percent had less

than high school education.

[Slide.]

This if more of I believe of what Dr. Boyle presented with some slightly different questions. We took the group that was most like those blood donors, paper questionnaire versus audio and versus adjusted odd ratio where the multiple of the first column divided into the second. You can see that for this group of questions.

These are what Turner was looking at, was the provision of sensitive information that you get multiplier rates of reporting at 3 to 17 times as great with audio-CASI as you do with paper questionnaires.

Also, note the bottom line there, I don't know if many of you can see it, in our judgment, 18 of the 49 questions currently on the AABB Uniform Donor History Questionnaire are questions that are judged sensitive.

[Slide.]

The authors of a related group, Cooley, as a senior author on that, set out the advantages of audio-touch screen-CASI as distinct from audio-CASI. Most of those, in fact, are audio-CASI

advantages. The touch screen advantages aren't only in two areas. The audio eliminates the need for the questions that are a requirement for literacy, the second bullet here.

The touch screen advantages relate to donor satisfaction and clean data files, and I don't think we want to go into clean data files right now, but I will answer any questions you want on that later.

[Slide.]

One of the things when I was talking about donor preference or user preference, users have a high preference. They found that users prefer the small sample, 108 STD clinic patients. Users preferred the A-T-CASI by a factor of 2 to 1 over keypad audio-CASI or interviewers.

Specifically, on privacy, they preferred it by a factor of 2 to 1, as well, and that was privacy of A-T-CASI versus A-CASI.

[Slide.]

We have, as I said, this QDS system, which is more appropriately referred to as Audio Video Touchscreen-CASI. We try not to make a commercial out of this, but we have the only data that is available on the technology.

It is headphone audio, touch screens, touch screens because no training is required. Everyone knows how to use their finger. It doesn't require you to miss a key ion a keyboard, for example.

It has on-screen text, AABB questions. It is tied into a staff review mode with flags for any question that is inappropriately answered, as well as electronic databases.

[Slide.]

The Mississippi Valley Regional Blood Center, adaptation of this technology. It has also been used in pilot tests at the Hoxworth Blood Center, which was published in the December issue of Transfusion last year.

It has been implemented at Mississippi Valley for a year now. It is at all nine of their fixed sites. We have utilized it in over 30,000 donor interviews. It is a product of 10 years of research and development.

[Slide.]

This is a picture of a staff member doing an on-screen registration as opposed to a keyboard registration, which is the most common, to illustrate that as an option. Staff do not use

headphones normally, those are for donors, but in the next screens that follow, there was no place to put headphones to emphasize the audio privacy.

[Slide.]

This is a standard format slide. There are 49 questions. They have the same format. The only thing that changes is the wording under the question, and the picture, which is selected to highlight some part of the question.

It took, by the way, a committee at Hoxworth three months to agree on what were socially appropriate pictures. Also, for purposes of bloodmobiles, the privacy feature is you can touch the center of the text area, and the text and the picture disappear, so that no one can know what response is being made, what question is being responded to.

[Slide.]

This is an example of a gay picture, to try and get at that behavior.

[Slide.]

This is IV drug use, to draw attention to that.

[Slide.]

This is to draw attention to Europe for

vCJD questions.

[Slide.]

This is a staff review screen. This note, the information goes directly from the donor's fingers to the review screen with nothing in between, no typos, no transposition errors. The computer highlights those questions that need review.

Those with green checkmarks need no review. Those with the yellow triangle are required to be reviewed before they can go on. Those with the yellow triangle plus a stop sign that you can see there were aberrant, were reviewed, reviewed aberrant, but not fatal. That is, they did not prevent the donor from donating.

The fatal or donor deferred is a big X that goes on that array. All of the questions highlighted in blue or the yellow triangle have to be reviewed before they can go on.

[Slide.]

This is an on-screen printout. It only occurs after the staff member has selected the print of accept or defer the donor, which you can see down there in the lower left side. At that time, the computer checks to make sure that all of

the logic is consistent and all of the questions complete before it can be printed.

Then, it must be signed by the donor. We can see here how legible it is by comparison. You don't have any problems with that with this technology. It is not dissimilar from a paper self-administered questionnaire except that it is all typewritten when it is done.

[Slide.]

The system was pilot tested at Hoxworth, as I said, various performance measures that we have used on the system, refusal to use it at all being perhaps the biggest one. We get almost no refusals. We have quit keeping track of it.

At the Mississippi Valley, we did 1,500 donor satisfaction surveys, which include privacy, clarify, truthfulness, time satisfaction, understanding, likelihood of donation again, which is a big one for us, and all of them are multiple factors of preference for the system, the audio video touch screen system versus face-to-face nurse interviews. Nothing less than a factor of 4.

[Slide.]

On the staff, we looked at that, much small sample sizes, however, staff prefer the

system to their own staff interviews by a factor of 3. They see it as faster for staff, donors more honest, answers more accurate, answers more confidential, fewer staff errors, and personally, much more satisfying to use than doing a face-to-face interview.

Also, Mississippi Valley has looked at three other areas - errors and omissions, and it has reduced those by at least 60 percent. Looked at time of donation. It increased the donor's time by 4 minutes and decreased staff time by 5 minutes.

[Slide.]

Significance.

[Slide.]

Our conclusions. Donor interviewing should include a verbal or audio component, and that new, unfamiliar questions in particular must be posed in one of these two modes. Also, the medical-scientific literature supports stronger guidance from CBER, encouraging the use of technologies that enhance understanding and honesty, for example, audio video touchscreen-CASI technology.

There is more information our web site. Any details of any these studies you want are

there.

Thank you for your time.

DR. NELSON: Thank you.

Questions? Comments? That was a very good presentation. It was very clear.

DR. ALLEN: How easy is it to integrate this system into the multiplicity of existing blood bank computer systems?

DR. CUMMING: We are working on that right now. It should not be difficult. It was designed to be integrated with paper. That is what most blood bankers wanted, but not in real time. That is, a batch kind of integration should not be a problem except we have to go to FDA and do a 510(k) to do that.

Committee Discussion and Recommendations

DR. NELSON: Dr. Williams, do you want to give us the questions again that you need our input on?

DR. WILLIAMS: Question 1. Does the committee agree that audio-CASI procedures are as accurate as direct oral questioning for eliciting blood donor medical/behavioral histories? Yes or No.

DR. SCHMIDT: Since we didn't hear

anything about the added use of illustrations or pictures until the very end, I am wondering if the question could be modified to say audio-CASI with illustrations or something. That is number one. Number two, since nothing ever gets validated including our responses, to be willing to change this question to instead of "are as accurate," "may be as accurate." I think you will get more from us that way by not nailing us down.

DR. KLEIN: Actually, I wanted to modify that a little bit, too, Paul, to say that the available data don't indicate that they are any less accurate than, because I don't think we saw data that could convince us that they are as accurate or not as accurate, but certainly what we saw and what we heard don't suggest that they are less accurate than what we are currently using.

DR. SCHMIDT: I accept.

DR. NELSON: Actually, we have been doing a study in Baltimore of injection drug users or largely, the literacy rate would be lower than hopefully the blood donor population, and we found that these people have been interviewed every six months dating back to 1989, and we recently introduced the audio-CASI system, and we found some

changes. We saw repeated declines in reports of injection risk behavior with some declines in incidence of new infections, but the declines in risk behaviors far outstripped what we found in the incidence.

When we went to the CASI, there was an increase in reported risk behavior, and also the drug users, they were happier. They thought this was a neat system. Now, it may be just that once you have been interviewed 12 times with the same questionnaire or a modification thereof, it becomes sort of boring and not very interesting, and this was the novelty of it, but it did work better.

The other thing we found was that sexual behavior was actually probably overreported by our male subjects on the interview. It was challenging were they still with it kind of, and when it went to the audio-CASI, the sexual behavior reports declined, and that sort of fit with what we found with STD reports over time.

So, I think that at least--now, these aren't blood donors, hopefully--but it did seem to work in this population that wasn't terribly literate. Now, they didn't have the same sort of pressures. In fact, you had to use drugs to be in

the study and you got money to come for your interview and blood drawing, so there were different incentives here than they would be if it were a blood donor.

I think in a variety of populations, this technology may be an improvement over interviews by thousands of different people maybe using a not so standard interview and not administering it the same way.

DR. EPSTEIN: I would like to follow up on Paul Schmidt's comment. Paul, I take your implicit endorsement of the visually enhanced system over audio-CASI per Sergeant, but I would rather see the question voted as written. The reason is that we refer to audit-CASI in our current guidance document, and if you were to, for argument's sake, vote in favor of the visually enhanced audio-CASI, we would left in a quandary what exactly you thought about it if it wasn't video enhanced, which is where we now are with the Red Cross system.

If you feel strongly enough that audio-CASI is not enough, then vote no, and you can comment on what you would consider sufficient, but I think we are going to end up with a muddy situation if we edit that question.

DR. NELSON: Good clarification.

Are we then ready to vote on this issue?

DR. SMALLWOOD: Voting will be taken by roll call.

Dr. Allen?

DR. ALLEN: The question, as modified, and with the understanding that we still need a lot of work, yes.

DR. NELSON: Just the may be as opposed to are, is that the modification?

DR. ALLEN: Yes. I preferred the no less accurate than, but I think what we haven't done, my personal feeling is I have got a little hangup with the term "accurate" since there haven't been any direct comparisons.

I am not sure that I really understand accuracy. Does the CASI method seem to defer donors with at least the same or higher degree of frequency? Yes. It is probably getting more accurate information, but the materials that were passed out, and I read the presentations I have heard, I don't have anything to do a direct, you know, I don't have a gold standard for what the answer should be from any of the people responding in the questionnaires.

DR. NELSON: I guess we know that, but the FDA is asking us a judgment call based on what is available.

DR. SIMON: I was going to see if this wording would work for both parties if we say the procedures are comparable to and get away from this word accurate that seems to be hanging up.

DR. NELSON: Do we want to take a vote on that?

DR. EPSTEIN: Okay. We accept that. Does the committee agree that the audio-CASI procedures are comparable to direct oral questioning for eliciting blood donor medical behavior.

DR. NELSON: That is an improvement.

DR. ALLEN: Yes.

DR. SMALLWOOD: For clarity, let me read the question as it has been modified.

Does the committee agree that audio-CASI procedures are comparable to direct oral questioning for eliciting blood donor medical/behavioral histories?

Dr. Allen.

DR. ALLEN: Yes.

DR. SMALLWOOD: Dr. Cunningham-Rundles?

DR. CUNNINGHAM-RUNDLES: Yes.

DR. SMALLWOOD: Dr. Davis.

DR. DAVIS: Yes.

DR. SMALLWOOD: Dr. Doppelt.

DR. DOPPELT: Yes.

DR. SMALLWOOD: Dr. Fitzpatrick.

DR. FITZPATRICK: Yes.

DR. SMALLWOOD: Dr. Klein.

DR. KLEIN: Yes.

DR. SMALLWOOD: Dr. Koff.

DR. KOFF: Yes.

DR. SMALLWOOD: Dr. Laal.

DR. LAAL: Yes.

DR. SMALLWOOD: Dr. Lew.

DR. LEW: Yes.

DR. SMALLWOOD: Dr. McGee.

DR. McGEE: Yes.

DR. SMALLWOOD: Mr. Rice.

MR. RICE: Yes.

DR. SMALLWOOD: Dr. Schmidt.

DR. SCHMIDT: Yes.

DR. SMALLWOOD: Dr. Stuver.

DR. STUVER: Yes.

DR. SMALLWOOD: Dr. Fallat.

DR. FALLAT: Yes.

DR. SMALLWOOD: Dr. Harvath.

DR. HARVATH: Yes.

DR. SMALLWOOD: Dr. Nelson.

DR. NELSON: Yes.

DR. SMALLWOOD: Dr. Simon, how would you have voted?

DR. SIMON: Yes.

DR. SMALLWOOD: There was a unanimous yes for Question No. 1, and the industry representative agreed with the yes votes.

DR. WILLIAMS: Question 2. Does the committee believe that for first-time donors self-administration procedures other than audio-CASI are as accurate as direct oral questioning for the entire donor questionnaire?

DR. SIMON: Shall we change this one to comparable, too, also?

DR. NELSON: Yes, change it to comparable.

DR. WILLIAMS: That works.

DR. NELSON: So, now you are talking about a paper theoretically, the standard donor questionnaire filled out not using CASI, but self-administered essentially, right?

DR. WILLIAMS: It would include paper and I guess, by implication, would also include a non-audio-CASI, would include a video

administration of the questions as currently worded.

DR. SCHMIDT: Was comparable accepted or not accepted?

DR. NELSON: Yes.

DR. WILLIAMS: Yes.

DR. FALLAT: Another comment. It was clear from the presentations that even the self-administered questionnaire involved additional interaction, and I think that should made clear that we are not approving just a self-administered questionnaire, but the self-administered questionnaire with the appropriate additional interactions.

DR. NELSON: Yes, you referred to it one time as secondary, what was it, secondary contact, or something? In other words, you don't just hand them a piece of paper and collect it, but follow-up questions, whether or not they are ones that should be standardized like the Red Cross four questions or whether there should be something else, but some contact with regard to the--

DR. WILLIAMS: As I mentioned, the current draft guidance that it out there asks that within the blood center SOP there be an effort to assess

comprehension of the questions to be defined within the SOP and asking did you understand is one way to approach that.

DR. NELSON: So that would remain as recommended as mandated or something.

DR. WILLIAMS: That is the current thinking.

DR. LEW: Can I just get clarification that the data that the Red Cross showed us did not really look at first-time donors, I mean separately, that it was just kind of all lumped together looking like the controls looked like those that got the self-administered questionnaire looked the same, but again, they didn't take first-time donors to really look at that issue very carefully.

DR. WILLIAMS: That is correct.

DR. NELSON: The obvious reason why this may be a separate question is the donor who has been in many times and may be familiar with the questionnaire, and I think the committee had previously sanctioned this for repeat donors, so now we are moving into the issue of the first time somebody shows up.

Toby.

DR. SIMON: I thought that Dr. Boyle's presentation to some extent addressed this in that the first-time donor might be even more likely to find embarrassment or concern and appreciate the more private setting.

I guess from the presentations that were made, I thought in some ways the literacy presentation took us a little bit aside from some of the major concepts, because I think the concern that people don't understand the words would be the same for self-administered or one that is being given verbally.

The advantage, obviously, the verbal interview is that a highly skillful interviewer like we would think of, some of us who are physicians trained in internal medicine, who are schooled in the arts of taking history, recognize that there is ability to elicit information, but here we have an interview being given 13, 14 million times a year in the United States, and from the presentation of Dr. Boyle, that I gleaned from that, is that even under circumstances of well-trained interviewers in a systematic way, it is a very difficult to eliminate the interviewer effect on the results, and therefore it would

appear that particularly with potentially embarrassing information, that the self-administration would be at least comparable even for the first-time donor in eliciting the kind of information that we want in terms of behavior.

So, I obviously am speaking in favor of the proposal. It is something apparently FDA has already allowed, I guess, the Red Cross to do, and it is something that has been tested by the Task Force, and it would seem that given that we are in the status where the interview that is given orally has not been completely validated, but from the information that we have, it would appear that self-administration is comparable.

DR. SCHMIDT: I would like to point out the word "comparable" doesn't mean a thing here. It comes from "to compare," saying we are able to compare it as either better, worse, or the same. It is not assisting you at all, Jay, to say something is comparable.

DR. NELSON: Maybe equivalent is a better word?

DR. FALLAT: I would agree with Dr. Lew that we really don't have data on first-time users, and I think it is very difficult to make a strong

statement with regard to first-time users.

DR. NELSON: Right. I think what we are being asked is without any validation studies, does it seem like we can get the information, the same information by the self-administered.

DR. FALLAT: Suggesting we use the term "seems like it's."

[Laughter.]

DR. ALLEN: I think that is important. My initial response, if I am looking at it strictly from a scientific perspective, the answer is I haven't seen the data, and I was going to vote abstain, and then I reread the question and it says, "Do the committee members believe," well, my gut feeling is that probably a self-administered questionnaire other than audio-CASI could be as good, may be better under some circumstances than some of the interview questions, because I have had some donor interviews where I don't think anybody was paying attention to my facial response, my body language, or anything else. All they wanted to do was to get through the questionnaire as rapidly as possible.

I don't think that those are effective methodologies either. So, if the answer is in the

absence of evidence, do we think that the self-administered questionnaire can be administered at least as successfully as a reasonably good interview, I will be willing to vote yes on that one.

DR. FITZPATRICK: I think, Alan, in the first draft, the draft required oral questioning of first-time donors in the first draft guidance.

DR. WILLIAMS: The draft guidance that the current draft, yes. It recommends oral questioning, and the intent of that recommendation, although there appeared to be some confusion, was for the high risk questions and the complex travel, and high level terminology questions.

DR. FITZPATRICK: So, making a leap here, if the committee responds yes to that, it provides FDA some basis for changing that recommendation for oral questioning of first-time donors.

DR. WILLIAMS: That's correct.

DR. FITZPATRICK: And that is kind of really what you are trying to get at here?

DR. WILLIAMS: That's correct.

DR. FITZPATRICK: In the comments that you received to the draft guidance, since we weren't provided those, how many comments addressed oral

questioning of first-time donors?

DR. WILLIAMS: Eight of the 12 addressed administration to first-time donors.

DR. FITZPATRICK: And what was the gist of those comments?

DR. WILLIAMS: I believe virtually all eight made the point that they didn't feel that the data supported a recommendation that there be oral administration to first-time donors, and as I mentioned earlier, 2 of the 8 had some confusion about whether we were referring to the more difficult questions or to the entire questionnaire, and raised the issue as to whether, in fact, we were changing stance and those centers that had been approved for self-administered questionnaire would not need to redo their SOPs and have those reevaluated. The latter is not the case.

DR. FITZPATRICK: So, with the lack of data, we are being asked to just say do we believe that self-administering, which occurs in some centers now of medical history questions, and evidently by the Red Cross of over 5 million donors, is at least as good as direct oral questioning and CASI.

DR. WILLIAMS: Right. Two points, keeping

in mind number one, that approvals for that process were based on submitted data, and number two, you asked what would the changes be.

One would be the draft guidance. Two would be a change in the earlier memorandum requiring oral questioning for the high-risk donors applicable to centers that have not submitted data to support a change to the self-administration.

DR. HARVATH: Alan, I would like to ask one question, and this is procedural. In your opinion or in your experience in reviewing such data, does FDA, have they received sufficient data on this specific question, because in my opinion, this could be a very interesting research question in certain settings.

I think in view of what you have heard of the data presented by Paul Cumming, what I would like to ask of FDA is if the answer to this question is yes, would FDA then still require or require data from individual centers to support such an approach, or would there not then be the need for any further data submission?

DR. WILLIAMS: Well, number one, I am not sure I am allowed to have an opinion, but I think were the committee to vote yes on this question, it

would certainly be considered very seriously in the agency's deliberations, and we would still independently review the extant literature and make an internal decision, but obviously, this is our advisory committee and we would weigh it very heavily.

DR. HARVATH: Has the committee seen all of the available data to help us specifically address this question?

DR. WILLIAMS: To the best of our knowledge, yes, there are data coming from many different aspects that are not directly comparing oral versus self-administered in a blood donor setting comparing first-time versus repeat donors. Those studies just don't exist currently, and as Dr. Boyle referred to, you are sort of making assumptions applying studies that don't quite meet the correct target to apply that to a blood donor situation.

A blood donor interview is not a survey, it is a social interaction to determine eligibility for health activity that a donor usually very much wants to be successful at, so I think it's a different situation. There are a lot of complications that aren't captured in any single

study.

But to answer your question, we would review all of the extant literature in addition to the committee's recommendation.

DR. NELSON: Can we vote on this? I wonder if we could--as accurate as, or as inaccurate as, whatever, the equivalent, that we use "other than audio-CASI are equivalent to direct oral questioning?"

DR. KLEIN: I still like the term "comparable" since equivalent means something different.

DR. NELSON: I think the issue Paul was making was they may be comparable, but much worse or much better, and I was using "equivalent" to mean equally good or bad.

DR. KLEIN: I don't think we have seen any data to tell us that they are equivalent. I think the data that we have seen does not suggest or indicate that a self-administered questionnaire is worse and that data that Dr. Boyle presented from other areas where sensitive information is gotten by questionnaire suggests perhaps that from a privacy standpoint, self-administration has some advantages.

DR. NELSON: Well, if we change it to comparable, does that help the FDA?

DR. FITZPATRICK: Paul brought up a good point, but how about "at least as effective as"?

DR. NELSON: Well, that is why I said "equivalent."

DR. FITZPATRICK: Which doesn't really say a whole lot either.

DR. WILLIAMS: And he has to be careful, the semantics aren't as important as the gold standard that you are talking about.

DR. CUNNINGHAM-RUNDLES: What is the verb of that sentence going to be? I am going for "may be."

DR. KLEIN: We can't design the question. The question is coming from the FDA. They have got to tell us what the question is. They have heard the discussion.

DR. NELSON: I think the issue here is in the first question, we said that CASI is equivalent or whatever, comparable to oral questions. Here, we are talking about first-time donors and we are talking about another self-administered questionnaire other than the CASI, so there are two differences in this question, first-time donors and

another form of self-administered question, right?

DR. WILLIAMS: Correct.

DR. DOPPELT: When you say it's non-audio-CASI, but it is some written self-administered, is it this form or are we speaking about a form in general?

DR. WILLIAMS: The intent is to move forward with a standardized questionnaire, which is reflected by the revised Uniform Donor History Questionnaire, which you have.

DR. NELSON: But this form might also be modified in the future to add other things to sort of embellish the jaundice, you know, I mean the earlier form had I think jaundice or yellow, I mean it had some other descriptors other than just jaundice, and I think the same thing is true for CJ disease.

DR. WILLIAMS: That is correct, but I think the comment goes to content and due to funding and other reasons, one can't basically beat the content issues to death. I think the Task Force, at the last meeting, described the process that was used to determine what wording was optimal based both on focus groups and one-on-one interviews and arrived at the wording that is in

the questionnaire, so I think basically, the wording that is there except for consideration of new questions that might be necessary, should be the wording that is considered.

DR. DOPPELT: I just wanted to point out, you are sort of voting on two concepts here. One is the concept of the written exam being comparable, equal, whatever you want to describe it, and the other is over time, as the questions may change, you are dealing with a different product.

DR. NELSON: Well, I don't think we are worried about the over time, we are worried about the first-time donors as being different from people who have been questioned before with a similar questionnaire, and we are worried about the method of arriving at the answers either, interviewer or questionnaire.

The donor questionnaire will change over time, there is no doubt about it, but we can't anticipate that.

DR. EPSTEIN: Paul said he would like FDA to state the question for the committee. I think that the question revised to ask, "Does the committee believe that for first-time donors

self-administration procedures other than audio-CASI are comparable to direct oral questioning for the entire donor questionnaire?"

There are many nuances and we could debate the language a lot, but I think most people understand what we are saying when we ask that. What we are saying is would you be just as satisfied if people are handed a piece of paper to self-administer the questionnaire versus audio-CASI or direct face-to-face, because you answered in Question 1 you would accept audio-CASI as the equivalent, so what we are choosing between here is face-to-face or audio-CASI deemed as comparable versus something else, which for the most part is a written self-administered questionnaire.

So, what we are saying is that okay, in general, we think audio-CASI and direct oral questioning are equally acceptable. Do we think that for the first-time donor we should be more scrupulous about just a written questionnaire? That is the intent of the question.

Again, if anyone is confused, I would be happy to try to clarify it further, but that is what we are trying to get at, because we are saying other than audio-CASI, and what is the common

practice other than audio-CASI is to hand people a written questionnaire.

DR. FALLAT: Would you be willing to use "may be?"

DR. EPSTEIN: Yes, I would be willing to do that.

DR. LEW: Can I just ask, all the stuff that we reviewed, was there ever one study that showed in blood donors that face-to-face was not as good?

DR. SIMON: I think Dr. Boyle had such studies, didn't he?

DR. LEW: No.

DR. WILLIAMS: Not in the blood donor setting.

DR. EPSTEIN: I just want to make one comment about "may be." I would be willing to make that change because I think that there is a general sense that committee members are more comfortable with that change, however, it then begs the question of whether FDA is going to want additional data, because if you say "may be," it implies that sometimes it is enough and sometimes it is not enough, so it leaves us in a quandary of, well, when do we decide it is not enough, and that is

sort of the problem that we have right now is deciding that it's not enough, but again I think at some level it would be helpful with that change to have the question voted if it's too confounding otherwise.

DR. NELSON: I sort of partly come down with Dr. Boyle in that I have donated several times, and I can say that sometimes the person doing the interview has worked there for a week or two, and has to do all kinds of different things in addition to take the interview.

I am not sure, I mean the written instrument is more standardized, and if it is accompanied with some sort of contact about the questionnaire after it has been done, I think it probably is an improvement, but it's hard to know that over 13 million donations. That is what we are being asked to determine.

DR. ALLEN: Which is exactly why, I guess I would like to ask Jay, what is the right answer if we want to encourage the FDA to look at this question very carefully. I think it's an important question that needs to be studied, and I am willing to be--I think there is sufficient data although it is certainly not definitive to suggest that the FDA

should allow a variety of different options at the present time while some definitive studies are underway, perhaps as part of definitive studies, but I really would like to encourage additional evaluation, careful evaluation of this question. I think it is a very important question.

DR. EPSTEIN: Well, if we revise the question, that audio-CASI may be comparable to direct oral questioning, on your proposal you would vote yes and then you would make the comment you just made, which I think we have heard anyway.

I think in the interest of moving to voting, I would accept the revised question, that then audio-CASI may be comparable to direct oral questioning. I would be happy to read it in its entirety again.

MR. RICE: The question already has the word "believe," it is not asking us that we know, but we believe that it's comparable. So, I think the word "believe" kind of alleviates the fact that we are not necessarily making a fact.

DR. EPSTEIN: But again I think the nuance here is if we change it to "may be comparable," and you vote yes, you are saying sometimes it might be and sometimes it might not be, so you are sort of

leaving the FDA with the difficulty of figuring out when it is acceptable and when it isn't, whereas, we are trying to make a policy here for the U.S. blood system.

As I said before, it leaves the FDA in a more difficult position, but if the committee is not able to vote the question of whether procedures other than audio-CASI are comparable, so be it. I mean if you can't vote that question, let's pose a question you think you can vote.

DR. LEW: If I can just ask, because Terry brought out the idea of believe, I think the problem is that it is one thing to say if you believe someone is guilty of a crime and it's just I believe, but you know there is consequences to saying I believe, then, I think we are all strict on ourselves.

I like the change of "may be" because I think we could feel more honest in saying what we truly believe.

DR. NELSON: So, what is the question now we are voting on?

DR. SMALLWOOD: The question as modified: Does the committee believe that for first-time donors self-administration procedures other than

audio-CASI may be comparable to direct oral questioning for the entire donor questionnaire?

Voting by roll call.

Dr. Allen.

DR. ALLEN: Yes, and it's an issue that needs additional study.

DR. SMALLWOOD: Dr. Cunningham-Rundles.

DR. CUNNINGHAM-RUNDLES: Yes.

DR. SMALLWOOD: Dr. Davis.

DR. DAVIS: Yes.

DR. SMALLWOOD: Dr. Doppelt.

DR. DOPPELT: Yes.

DR. SMALLWOOD: Dr. Fitzpatrick.

DR. FITZPATRICK: Yes, and I support Dr. Allen's comment.

DR. SMALLWOOD: Dr. Klein.

DR. KLEIN: Yes.

DR. SMALLWOOD: Dr. Koff.

DR. KOFF: Yes.

DR. SMALLWOOD: Dr. Laal.

DR. LAAL: Yes.

DR. SMALLWOOD: Dr. Lew.

DR. LEW: Yes, and I support Dr. Allen's comment.

DR. SMALLWOOD: Dr. McGee.

DR. McGEE: Yes.

DR. SMALLWOOD: Mr. Rice.

MR. RICE: Yes.

DR. SMALLWOOD: Dr. Schmidt.

DR. SCHMIDT: Yes.

DR. SMALLWOOD: Dr. Stuver.

DR. STUVER: Yes.

DR. SMALLWOOD: Dr. Fallat.

DR. FALLAT: Yes.

DR. SMALLWOOD: Dr. Harvath.

DR. HARVATH: Yes.

DR. SMALLWOOD: Dr. Nelson.

DR. NELSON: Yes.

DR. SMALLWOOD: Dr. Simon, your opinion?

DR. SIMON: Yes.

DR. SMALLWOOD: There was a unanimous yes vote to Question No. 2. The industry representative agreed with the yes vote. Just for the record, there are 16 members eligible to vote.

DR. NELSON: Let's see if we can get lunch, and if we could get back around 2:30, 2:35, because we have got two issues to discuss this afternoon.

DR. WILLIAMS: Our thanks to the presenters and to the committee. It was a

difficult discussion.

[Whereupon, at 1:50 a.m., the proceedings were recessed, to be resumed at 2:30 p.m.]

AFTERNOON PROCEEDINGS

[2:15 p.m.]

DR. NELSON: We are a little over an hour and a half behind. In the past, the way we have dealt with that is continued to meet until about 9 o'clock at night or something like that. Obviously, we can't do that today because it's a one-day meeting, but what we are going to do is we will have the presentations on the Chagas disease and then there were some people that wanted to comment on Chagas and others that wanted to comment on the testing who had come here specifically for that.

In the possibility that we won't finish everything by 5 o'clock, we will accept, during the open public hearing, comments on either one, but we hope you will be brief enough that we can get through the whole program, and we might be able to finish by close to 5:00 at any rate.

The first discussant on Chagas disease, Update on Testing for Chagas disease, the Latest Trends in Transfusion-Transmitted Chagas, David Leiby.

DR. DUNCAN: Dr. Nelson, I am Dr. Robert Duncan from the Center for Biologics, Division of

Emergent Transfusion Transmitted Diseases, and I just wanted to say a few words about why we are bring this informational session, and then Dr. Leiby's presentation.

DR. NELSON: Okay.

Introduction

Robert Duncan, Ph.D.

DR. DUNCAN: Recently, it was brought to our attention that there is little activity among manufacturers working to develop a marketable blood screening device to test for Chagas, and it is our intention that this presentation might help to provide some stimulus for manufacturers.

I would like to give just a little bit of background to illustrate why we think it is important at this time.

[Slide.]

This is just some of the background about the current state of Chagas disease in this country. David Leiby's presentation will go into these points in detail, but there is just a couple of things that I wanted to highlight.

Clearly, it is a disease that is affecting a lot of people in this hemisphere. It has been recognized as a problem for blood transfusion in

the endemic areas. There are six cases of transfusion transmissions have been documented, and there are three cases of solid organ transplant transmission.

The seroprevalence in the U.S. population has a low range, which mainly has to do with the proportion of immigrants from South and Central America, but increasing rates of immigration raises the concern about the potential for increased transmission, and it is this concern that has been coming to our attention.

[Slide.]

At the present time, there is no serological screening of donors recommended due to the low prevalence and to the fact that there is not a suitable test. Questions of sensitivity and specificity and availability are all still on the table, and the blood supply is, however, being protected with the donor questionnaire, and we have had a lot of discussion about the donor questionnaire, so we know the importance of that and also the successful rate of that.

At the present time, there are Chagas tests that have been licensed for use in diagnostics, but not for blood donor screening.

Those are enzyme immunoassays and radioimmune precipitation assays.

Some of the questions of suitability also have to do with having a complete testing system that could be effective in the blood donor screening setting.

[Slide.]

I want to just retrace a little bit of the history of the question of the Chagas test vis-a-vis CBER and the Blood Products Advisory Committee.

In 1989, the advisory committee recommended donor screening for Chagas provided there were a suitable test. We came back in 1995 with a question about the tests that were available at that time, and posed the questions are the available tests appropriate for donor screening.

The response of the committee was three was voted yes, zero people voted no, and 10 abstained. So, clearly, there was no consensus on the committee for use of the tests that were available at that time.

Part of the problem was that multiple tests were presented at the same time with slightly different technologies, but also there was a

problem of CBER not coming forward with a clear set of standards for what would be an approvable test for blood donor screening.

In the 1995 BPAC, there was also the request that there be a serious approach to the question of what are the implications of a false positive rate in a universal donor screening setting, in other words, would be generating more false positives than true positives potentially. So, that is also an important issue.

With this kind of background, to understand why we are bringing the information forward at this time, I would like David Leiby to come up and make his presentation regarding the current seroprevalence and transmission of Chagas.

Latest Trends in Transfusion-Transmitted Chagas Disease

David Leiby, Ph.D.

DR. LEIBY: I was asked by Hira Nakashi to come here and at least provide an update on the latest trends in transfusion-transmitted Chagas disease.

[Slide.]

The first slide actually gives you some characteristics on Chagas. First of all, it is a

protozoan parasitic disease caused by a flagellated parasite called Trypanosoma cruzi.

It is a parasite that is endemic to the Americas only in Mexico, Central America, and South America, although rarely it actually occurs in the United States. Some of you may not know that, as well. There are at least four or five autogenous cases reported in the U.S., one about a year and a half ago in the State of Tennessee, so the bugs themselves and the parasites are here in the United States.

[Slide.]

This is very important. It causes a chronic, asymptomatic, and untreatable infection. So, when one thinks about blood donors, we are talking about individuals that are infected for life, so their whole life they are blood donors, they may transmit the infection.

They are asymptomatic , so when they present as blood donors, you do not know that they may be infected. Lastly, there is no suitable treatments for Chagas disease, so this is an infection that is, as I said, life-long, asymptomatic, and untreatable, and in 20 or 30 percent of the individuals with chronic infections,

they develop a rather debilitating disease that can lead to death.

Transmission is by four primary methods - vectorial, and I will show you the bug in a second, congenital transmission, which has some relevance to blood banking, organ transplant seems to be the popular way to transmit diseases these days, and I will mention that, as well, and, of course the one we are most concerned about today is blood transfusion.

[Slide.]

This is a picture of the reduviid bug, which is the one that commonly transmits Chagas disease in the natural form, vectorial transmission, and it is not transmission by the mouth part, it is transmission by the back end.

The parasite is found in the infective stage, or the trypomastigote is found in the feces of the bug, so during the course of a blood meal on an individual, the bug fills with blood, defecates, and then the feces containing the infective stage is either rubbed into the bite wound or, in the case of this young girl, into the eye or into any other mucosal surface.

This is a reaction, a chagoma. It doesn't

happen all the time, but it is a swelling at the site where the parasite enters the host. The ultimate location where the parasite lodges is in the cardiac tissue, and that is where it has its most significant pathological occurrence.

It is there that it can sit quietly for 20 or 30 years. Individuals do not know they have the disease, and then later on, in their fifties, they may die suddenly, a sudden death, and may have congestive heart failure or several other problems that can lead to their demise.

[Slide.]

Well, why, if I said, if it is primarily a disease of Latin America, why are we so concerned here in the United States? Well, quite obviously, it has to do with immigration and later with demographics.

Over the past 20 or 30 years, there have been millions of individual who have immigrated to the U.S from Mexico, Central America, and South America, largely for socioeconomic issues. This is just some data that came out of the 2000 census, and these are only individuals who report their country of birth as being in Mexico, Central America, South America, and there was over 12

million at that time. This certainly does not include illegal aliens, which also donate blood, so this number is considerably larger.

In fact, if you look at the most recent census data, and you look at the Hispanic population, you can see there is a 60 percent increase from 1990 to 2000, to some 35 million. I am not here to tell you that all 35 million are potentially at risk, but what it tells you is that the Latino population continues to increase because more individuals are immigrating.

This brings up the issue of congenital transmission, which is the transmission from the mother to the unborn child. We have seen several cases in some of our studies, and I will mention those later. So, we have to be concerned as far as Chagas disease in this country, not only about the first generation of immigrants, but also the children and perhaps even the children's children.

[Slide.]

This is from a case we described in 2001, and the similarities of this and the recent case in West Nile are somewhat striking. In this case, there is no blood transfusion, I don't think we know that yet about West Nile either, but this is a

case in 2001 in which there was Chagas disease after organ transplantation.

There was a single donor, single cadaver donor in which multiple organs were removed and placed into three recipients. There was a kidney and pancreas in one, a liver in another patient, and the last recipient received a kidney.

This first individual, the kidney-pancreas came up positive on a blood smear. This is the actual blood smear. To see four parasites in a single blood smear is rather phenomenal.

This individual died of acute Chagasic myocarditis, so from one recipient, we see three individuals being infected. Part of the story that I don't think is included is that when they looked at this cadaver donor, they also considered taking the heart, but upon looking at the heart, they noticed that there was a lot of pathology associated with the heart, so they did not transplant the heart fortunately. So, from a single case, we see three.

[Slide.]

In the United States, as Robert mentioned, there have been six transfusion cases, transfusion-transmitted cases since 1987. There

are a couple of things that I want to point out. First of all, if you look at the donor, in this case Mexican, Bolivian, Paraguayan, Chilean, German/ Paraguayan, who is a young child born in Germany, migrated to Paraguay with his parents, they are mennonites, when he was very young. But five of the six that we know of, the donors came from endemic countries.

The other thing to notice is that these individuals who were infected by transfusion are not people who live in Miami, Houston, or Southern California. Some live in New York City and, quite surprisingly, there is two from Manitoba. So, it is a disease that affects individuals not only in the southern part of the United States, but in all regions.

I am not going to stand here and tell you that if you live in Los Angeles, you have the same risk as someone in Minneapolis, but the point is that there are probably positive individuals anywhere in this country and Canada. You just may take longer to find them in the more northern climates.

[Slide.]

The question always comes up when I talk

about Chagas, and this is a question that is actually very fair, is why are there so few transfusion cases. I am going to show you data on seroprevalence that shows it occurs quite frequently. So, why don't we see more than six transfusion cases?

What I would like to propose and tell you is that those reported cases are, in fact, the sentinels. Those are the ones we pick up and the ones we know about, but, in fact, there is many more cases that go on.

Those six cases in all those individuals, they are fairly severely immunosuppressed. They actually had fulminant disease and it made it very easy to identify that they, in fact, had Chagas disease, and as I said, it was easily detected and diagnosed.

So, what is really probably happening is that there is many cases that are missed. We have immunocompetent individuals. As I said, this infection is asymptomatic, we would not recognize it.

They are often misdiagnosed. The acute infection is rather--the symptoms are flu-like, probably easily missed even if they did have the

infection. So, lastly, they are not recognized. So I would say that while there are cases which are very clear, there are many which we probably miss. This poses the risk that perhaps 20 or 30 years down the road, when these individuals develop cardiac complications, that is when we will know that they have been infected by blood transfusion.

[Slide.]

Just to show you that we really miss these individuals, this is a study I actually did our chairman, and we looked at cardiac surgery patients, and we were curious about looking at transfusion issues, but what came out of this was something I think in some ways is more important.

This comes from the fax repository, which is a pair repository of cardiac surgery patients that have a preoperative sample and a postoperative sample. So, in this repository are over 11,000 multiply transfused patients that we tested by EIA. We found out of that that 6 of them, or 0.05 percent, are actually confirmed as seropositive. That was postoperatively.

Then, you have to go back and check the pre-op sample to see if they got the infection from the blood transfusions they received during

surgery. Well, we found right off the bat that 4 had preoperative samples, which means they didn't get it from transfusion, they had it before they had surgery.

Now, two preoperative samples were not available for us to test, however, those two individuals had both received heart transplants, and the tissues, the excised tissues from these hearts are still available and maintained in blocks, and when we did PCR on those, we found that both the hearts were also positive by PCR. So, all six of these individuals had Chagas before their surgery.

Five of the six individuals were also Hispanic, and if one looks at the demographics in this repository, we find that 2.7 percent, let's say 3 percent for today's purposes, 3 percent of Hispanic patients in this repository were seropositive for Chagas disease.

What was most interesting is when you looked at the medical records of these individuals, individuals that were Hispanic, individuals that had congestive heart failure, arrhythmias, other symptoms of Chagas, not once were they tested for Chagas, so by and large, the medical community is

not recognizing this, they are, in fact, missing it.

[Slide.]

Some of our data from our studies that were recently published, I believe in Transfusion in May, in our studies in Los Angeles and Miami, there is Red Cross Studies, in Los Angeles, they included over 1.1 million donors, in Miami it was 181,000.

Donors at the blood centers were asked a very simple question: Were you born in or have you spent more than six months in Mexico, Central America, or South America?

When we asked that question, in Los Angeles, 7.1 percent of individuals responded yes, while in Miami, it was 14 percent. Some individuals many years ago, I don't think people are proposing this anymore, suggested that perhaps we could just ask that question, and based on that question, defer blood donors. Well, I don't think any blood center in this country would be willing to defer 7 to 14 percent of their blood donors.

If you follow through with this testing through the EIA, and then by RIPA testing, which was the confirmatory assay we did, in Los Angeles,

about 1 in 7,500 donors are positive, are seropositive for Chagas; in Miami, it was about 1 in 9,000. That is overall donors.

[Slide.]

What became very interesting is when you take that Los Angeles data and you look at it year by year, this is 1967, '97, and '98 is kind of covered here, this is percent donors positive. Those are hard numbers to work with, let's work with these numbers on top of the bars.

In 1996, in Los Angeles, 1 in 9,900 donors were positive for Chagas. In 1997, 1 in 7,200 donors were positive. Finally, in 1998, 1 in 5,400 donors were positive. That is a very high significant difference each year increase.

So, what does that increase mean, what is really going on?

[Slide.]

First of all, let me tell you that in this study, all EIA-positive donors are deferred regardless of their RIPA test result. So, if they were EIA repeat reactive RIPA-negative, they were still deferred. So, we are pulling out any donor who is either positive or even repeat reactive, so we are not counting the same donors over and over,

we are actually pulling out of the pool, so there is actually fewer positives available.

There is a significant increase in rate each year, but what is more important, and these are directly related, there is a significant increase in at-risk donors each year, so as there is more at-risk donors, there is a greater likelihood of finding positive individuals.

What we found was going on in Los Angeles was, in fact, there was an advanced minority recruitment efforts specifically targeting the Hispanic population, and this was really the gist of the paper we published in May, that as we begin our donor demographics, as we begin to change who we are recruiting for blood donation as per that earlier census data, that shows you the great increase in Hispanic population, we are going to encounter more individuals who are seropositive for Chagas.

[Slide.]

At the same time, from that same study, we also looked at different donation characteristics by the type of donation, allogeneic, apheresis, and directed. As you can see, by and large, most of the donations were allogeneic, 991,000, 93,000 were

apheresis, and we had 18,000 directed.

If you looked at the number of positives, for Chagas, we see that it was 138 allogeneic, 1 apheresis, and 8 directed. If you look at the rates, they became rather startling, 1 in 7,200 for allogenic, 1 in 93,000 for apheresis, 1 in 2,400 for directed donors.

This then goes back to the same thing I said before, it goes back to the at-risk population, and those are the people who responded yes to our question, 7.5 percent for allogeneic, only 2.6 percent of the apheresis donors were at risk, but 10.2 percent of the directed donors were at risk, and there is a relationship between higher levels of directed donation among Hispanic populations which helps to explain this rather high rate.

[Slide.]

The other thing I am often asked about is why in our lookback investigations, we found zero out of 19 transmitting infection, so I will use a baseball analogy since they didn't go out on strike.

Why are we 0 for 19? Not a very good percentage. I want to say a couple things you have

to keep in mind. First of all, transmission by blood transfusion does occur. It occurs in this country, it occurs throughout Latin America. Chagas is tested for in all the countries of the Americas with the exception of Canada and the United States. In fact, transmission in South America is reported to be anywhere between 13 and 49 percent, so why don't we see it here more often?

Well, some have proposed maybe these donors are only antibody-positive, they are not parasitemic. Well, in some studies we have done at the CDC, and presently writing up for publication, we observed that 33 of 52 percent seropositive donors were, in fact, parasitemic by PCR, so not only are we transfusing blood that is antibody-positive, in over the half the times they also have parasites.

But what is interesting, though, is when you test these donors, we find that the parasitemia is, in fact, intermittent. Not every time you sample them can you demonstrate by PCR that they are positive. Part of that is due to the intermittent nature of the parasitemia in the human host, it is also issues about sample size, how big a sample you take in testing, as well.

The other thing I want to point out is which products, of these 19 individuals, what products were involved? Well, 11 were red cells, 3 were fresh frozen plasma, 2 were cryoprecipitate, and 3 are platelets. This is where we think the answer to this issue is.

[Slide.]

We think that perhaps that platelets are the ones or the component that may play the greatest role, at least for Chagas. We base that on at least 5 to 6 reported transfusion cases in U.S. and Canada involved platelets. We don't know about the other ones, so we can't say 6 out of 6, but we know five to six were.

Platelet recipients in general are more likely to be immunocompromised. It gets back to that statement I made earlier about the sentinel cases. Also, T. cruzi, because of its buoyant density more likely may separate out with the platelets during whole blood centrifugation.

We have done some studies, and these are ongoing at the Red Cross and the home lab on survival in blood components. If we look a whole unit of blood inoculated with T. cruzi, it survives up to three weeks, and there have been some

Brazilian studies I think which show it goes much longer in certain kinds of blood.

In platelets, we are able to demonstrate viability up to four days, the product only is on the shelf for five, so that is mostly the whole product shelf life. Red cells appears to be only four days, plasma, I think the freezing process probably kills them.

So, we think the platelets, based on the data up here, and also their survival, may, in fact, be the component most likely involved, and because our lookback only really had three platelet units out of the 19, we probably haven't just looked at enough, so we think that it probably is going on a much greater rate than perhaps we think.

[Slide.]

So, what about nationwide risk, how big of a problem is this? Well, if we say there is 13.2 million donations per year in the country, and that includes all the blood centers, each donor gives about 1.6 times a year, so if we divide that number, we get 8.25 million donors in the U.S. per year.

Now, based on some surveys we did, we think about 2.5 percent of all the donors in this

country are at risk, so that leaves us with 206,000 at-risk donors, and when these donors are tested by some type of antibody test, and confirmed by RIPA, we find that 1 out of every 625 of those are found to be confirmed seropositive donors, so we feel there is about 330 seropositive donors in the U.S.

Now, again, if each one of those donates 1.6 times per year, probably about 528 seropositive donations per year in this country. Now, if each donated product has been made into about 1.17 components, we feel that there is probably about 618 potentially infectious components per year, and these are all estimates, and all these other numbers here are estimates, too, but it does show you there is a significant number of components out there.

[Slide.]

What about interventions, what can we do? Well, we have looked at question strategies, as I said, we looked at questioning strategies and published them through case-controlled studies, and these were designed to identify at-risk donors for deferral or perhaps for testing.

What we found, by and large, that these lack sensitivity. Most of the questions had to do

with birth or time spent in the country, some donors were uncomfortable answering the question because they thought we were getting at immigration issues, and the other problem with these questions is that they don't deal with the issue of congenital transmission.

What about blood screening? Well, I guess the reason why we are really here is that there is a lack of licensed tests. A couple of strategies we could talk about for blood screening, and I am going to point this out right upfront, that I really don't feel there is any value, added value in NAT screening for Chagas disease.

These are individuals who were infected perhaps 20, 30 years ago in their endemic countries, they have very high antibody titers, so we are not dealing with a recent ongoing active infection in the United States, we are dealing with something that occurred a long time ago. So, from the standpoint of Chagas, some type of antibody screening is probably sufficient.

What we would probably suggest is that universal screening may be the most beneficial way to go. Screening in certain locations in this country, geographical locations in the South, would

likely miss those infections. We already demonstrated transmissions that occur in New York City, Manitoba, or anywhere else.

Some have suggested that since this is a chronic infection something people picked up 20 or 30 years ago, not actively transmitted in this country, why not just test people one time. One time they test, and if they are negative, they can continue to donate blood.

We have looked at that issue and in some ways that becomes even more complicated. It gets to be a very difficult issue for tracking who to test, who not to test, and our feeling was there are probably more errors trying to track the donors in that format than just to screen universally.

So, we talked about one-time testing, but we decided that was logistically difficult and probably not cost effective, as I just explained, and then universal screening is what we think would probably be the easiest and most effective way to go.

[Slide.]

So, to summarize this, we know that seropositive donors are found nationwide, but levels vary based on the at-risk population, so

certainly places like Los Angeles are going to have more than, let's say, Minneapolis or Portland, Maine, but if you look hard enough, you can find them in most parts of this country.

There are no reliable risk factors, as I have said. Infections, keep in mind, are asymptomatic, chronic, and untreatable, and most importantly, they are congenitally transmitted.

Infectious donors are demonstrable, we do see transfusion cases, and likely universal screening is perhaps the best route to go.

Lastly, this is going to be an ongoing blood safety issue largely because of continuing immigration, and also because of the second and third generation, so it is not an issue that is going to go away.

Thank you.

DR. NELSON: Thank you.

Questions? Yes.

DR. LAAL: I just wanted to be sure I understood this correctly. You said that 20 to 30 percent of the people who get infected go on to develop disease, am I right?

DR. LEIBY: When individuals are infected, they go through an acute phase and then they enter

what is called indeterminant phase, and that is what most of the blood donors we see are in.

In the indeterminant phase, they generally have high antibody titers and intermittent parasitemia, 20 to 30 percent of those individuals go on to develop clinical manifestations whether it be cardiac or in some cases, depending on the organism, some intestinal complications.

DR. LAAL: But the organism does continue to survive in those 70 percent?

DR. LEIBY: Oh, absolutely, it is not an infection that clears. If you are infected, you are infected for life.

DR. ALLEN: Is there any screening being done in any of the Central or South American blood collection centers?

DR. LEIBY: Yes, there is screening throughout Latin America. I think they are in the process of implementing screening in parts of Mexico, it is done in most of Central America, certainly all throughout South America, the blood is screened, yes.

DR. ALLEN: The same basic tests being proposed here in terms of EIA with RIPA confirmation?

DR. LEIBY: Tests will vary throughout all those countries. In some parts of South America, for instance, they may do two tests, even three tests, and then depending on how many are positive, they will determine whether or not they are positive. I mean there is a variety of tests used throughout these countries, some are better than others.

DR. NELSON: I tried to get some information on this by calling Dr. Cruz at PAHO, and what he told me was that PAHO did some surveys of blood banks, which have been published and the latest data is from the year 2000, and Chagas is tested, as you say, in all Latin American countries.

In about six countries, all donors are tested including Brazil, Argentina, Paraguay, et cetera, I can't remember all of them, but there are a number of countries where only some donors are tested, and there is some where its testing is much less common, and that includes Mexico.

He said that in the year 2000, there some something over a million donors that were not tested for Chagas, there were about 65,000 donors that were not tested for hepatitis C, and there

were about 5,000 donors that were not tested for HIV in all of Latin America, and they have a foundation blood safety grant.

But when you come down to which test is used and how does it perform, apparently, it varies all over the lot, and some of them use tests that are licensed for diagnosis in this country, Abbott, Gall, and I forget the third one, but there are others, Organon, there are a number of others that are available, not licensed in this country, available only in Latin America, and there are some tests that are essentially home brews.

So, they are testing, and they recognize the importance of the problem, but in terms of the QC and how it is done, it is quite variable, but nonetheless, most blood bankers transfusion services in Latin America are highly sensitized to the importance of this problem and trying to do something about it.

DR. LEIBY: I think in many respects, it gets to the socioeconomic issues, where they can test. It might be the big cities as opposed to the rural Central American countries.

DR. NELSON: That was a very good summary.

Regulatory Pathway for Donor Screening

Robert Duncan, Ph.D.

[Slide.]

DR. DUNCAN: Again, speaking the point of view from the FDA, we are not bringing any question in this informational session. The FDA probably won't bring a question about Chagas testing before the advisory committee until we feel there is a test that is suitable for blood screening.

But towards development of a suitable test, we would like to present our current thinking on what the regulatory pathway would be for a Chagas blood screening device, and also what the standards for that suitable test might be.

So, the first point is that as a blood screening device, a Chagas test kit would be regulated under the Food, Drug, and Cosmetic, and the Public Health Service Acts. So, therefore, as it is regulated under those laws and those regulations, testing would be done with an investigational New Drug Application, and then marketing would require a biological license application.

Another point that we want to make at this stage is that any BLA submission for a device to screen for Chagas disease should include the

characterization of a confirmatory test. One kind of test would be required that could be used to screen a lot of different samples, but then a more rigorous test to confirm any positive samples would need to be characterized as part of the test.

[Slide.]

An IND submission for testing with a Chagas screening device that has the potential to contribute new scientific information leading to development of a licensed test is encouraged.

There is an issue about whether to do testing under IND simply as a means to ensure that blood products don't have Chagas disease being transmitted. Our point here is that we want a licensed test and that the intention of an IND is for development of a licensed test.

So, any IND submission has to at least contribute new scientific information that could lead to a licensed test, and any new sponsors that would like to submit an IND, we are asking you to come forward and write a draft proposal, discuss the IND with us prior to submission of the IND, so that the process can go quickly and more smoothly.

[Slide.]

I am going to talk a little bit about our

current thinking on standards for approval of a Chagas blood screening test. This is our current thinking. Ultimately, we will likely be publishing a guidance document and on the way towards writing that guidance document, we would probably sponsor a workshop inviting manufacturers and blood bank organizations, FDA, and other interested parties, to gather together accumulated wisdom before writing that document.

In reviewing the minutes from the 1995 Blood Products Advisory Committee meeting where Chagas was discussed, one of the major questions that members of the advisory committee had at that time was what are the standards, what are the standards for approval of the test, how can we decide what is a suitable test, you need to tell us what the standards need to be.

In the intervening years, we have gotten some accumulated wisdom from licensure and review of a number of blood screening tests for HIV and HIV diagnostics, and the numbers that I am going to present today are sort of the distilling of that experience.

I am going to talk in several specific areas, chemistry, manufacturing, and controls of

both crude lysates and well characterized antigens, clinical sensitivity, clinical specificity, analytical specificity, analytical sensitivity, reproducibility, and instrument and software.

[Slide.]

First of all, for chemistry, manufacturing, and controls, devices utilizing crude lysates, crude parasite lysates would have to have manufacturing controls to assure lot-to-lot consistency of antigen composition.

The kinds of things that we are recommending to achieve that kind of lot-to-lot reproducibility would be to generate a standard reference panel of sera that have varying degrees of reactivity, so that the product is tested both near the cutoff, as well as strong positives.

There should be something like a Western blot, an immunoassay to characterize individual antigens and that the reference panel of sera should show consistent representation of the immunodominant antigens in the parasite.

Lastly, endpoint titration curves from testing of the final product should have slopes and midpoints that fall within acceptable limits. It has been shown in this kind of immunological assay

that these features, the endpoint, as well as the slope, give an assessment of the quality, as well as the quantity, of the antigen present in that lysate mixture.

[Slide.]

I am pointing to a draft Points to Consider guidance document that is available from FDA. It was used related to HIV testing, but it is also an antigen preparation process, and there are a lot of QC procedures that are talked about in this guidance document that would be applicable to an antigen preparation for a Chagas lysate.

[Slide.]

Next, the more well characterized antigens. A number of manufacturers are moving towards recombinant protein and peptide antigens in a test kit. We would expect to see lot-to-lot consistency by amino acid analysis, peptide sequence, and there is a guidance document for biological in vitro diagnostic products that I would refer you to that is on the CBER web site.

[Slide.]

So, now on the question of clinical sensitivity, any products should be tested with at least 100 sera from clinically diagnosed

parasitologically positive patients. These are all presumed positives, so that any sera testing negative should be submitted to a confirmatory test, and our recommendation for the confirmatory test is the radioimmuno- precipitation assay. It has been characterized by the American Red Cross in David Leiby's lab, Dr. Kirkoff has developed it initially. It was used by Abbott in some of the testing of their product. So, it is a complex and technologically difficult assay, but it is extremely reliable and has the highest specificity, and it has been reproduced in multiple laboratories, so we feel that it is the best confirmatory test at this point.

The next step in terms of showing clinical sensitivity would be to do a prospective study with at least 500 samples in an endemic area, and we are suggesting that the prevalence in that area should be greater than 5 percent, the idea being that the product should be usable to test a range of samples that could be either positive or negative, but where a substantial number of positives will be found.

In that prospective study, each sample should also be tested by a reference test, and in

this case, our recommendation is the immunofluorescence assay, which has been well characterized by the CDC, be used as a reference test.

After these 500 samples are tested by the new test, as well as the reference test, then any positives, positive on either test, would be subject to a confirmatory test, again recommending the RIPA. This will be able to address the question of sensitivity of the test.

[Slide.]

Another very important point for a test to be used in a universal screening setting would be specificity. The device should be tested in the end user setting meaning in the blood collection setting, in the U.S. population. There should be at least three geographically separated sites with sufficient numbers for statistical power at each site, and 5,000 samples overall has been satisfactory in some of the other studies.

At least three lots of the device need to be tested in this large study. No reference test is required, in other words, every single sample does not have to be subjected to a second test, but positive samples are confirmed with the RIPA test.

[Slide.]

A couple points that are more in terms of the analytical quality of the assay itself. Analytical sensitivity, each lot of the device should be tested with a dilution series of a known positive sera to determine the limit of detection. That is more or less the same point I made earlier about the endpoint titration.

Then, the other recommendation here is that seroconversion panels, if available, should be used to test the device at the point of seroconversion when there might be limiting quantities of the antibody.

[Slide.]

Analytical specificity comes in terms of potential cross-reactivity. Well, there is two issues, cross-reactivity and interference. In cross-reactivity, the device should be tested with a panel of sera from patients with potentially cross-reactive infection, and some of the infections that have been identified, visceral leishmaniasis is known to cross-react with lysate samples of Chagas antigens, but malaria, schistosomiasis, syphilis are others that have been suggested to look for cross-reactivity.

It is known that influenza vaccinees soon after vaccination can cross-react with the Chagas test. Serum samples with autoimmune disease would also be potential cross-reactors.

On the question of interference, a Chagas-positive serum should be spiked into potentially interfering sera, and the final anti-Chagas antibody titer should be very close to the cutoff. I have listed some of the examples that have been looked at for other products for interference with the assay - hemolyzed sera, microbially contaminated sera with various anticoagulants, comparing fresh or frozen serum, bilirubin, high triglycerides or hypergammaglobulinemia.

These kinds of tests should be done one time in the preclinical phase of development of the product. This cross-reactivity could be included as a lot release comparison on each lot of the device.

[Slide.]

Then, we have the question of reproducibility and proficiency. So, as part of the IND and the BLA, a panel of at least five sera, comprised of both positive, negative, and weakly

reactive sera should be tested in at least three sites with different operators with at least three lots of a device.

Each study site which is going to be used should demonstrate proficiency with this panel before screening donors. So, the idea here, part of the device is to develop this panel of sera which could be used for proficiency testing in an ongoing way.

[Slide.]

So, a lot of the kinds of devices that manufacturers are talking about could be run in an automated setting, and this is to remind you that instruments and software used for screening blood are medical devices and must be developed and manufactured in accordance with the quality system regulation, which is Regulation No. 820 there.

There is a Center for Devices and Radiological Health guidance document called General Principles of Software Validation which may be used to assist in the software-related design control issues.

[Slide.]

Also, to remind potential sponsors that instrument and software is submitted as a separate

510(k) in a biological license application. There is also a Center for Devices and Radiological Health guidance on that question, the content of premarket submissions for software contained in medical devices, that describe how to do a 510(k) that is then linked to the biological license application.

There is another question that comes up in this process, which is, is the device of a major or a minor level of concern, and it has been determined that devices used for screening blood donors is a major level of concern, and you can refer back to the guidance to ensure the appropriate documentation that is required for an item that is of major concern.

So, that is the end of my summary of the kind of standards we would expect to see on a blood donor screening device for Chagas.

Any questions?

DR. NELSON: Any questions?

DR. KLEIN: Just a comment. This has been going on for a long time, and this morning we heard about a disease that is not known to be transmitted by blood, and should it be, would be probably asymptomatic in most individuals who would then

become immune.

Here we have a disease that we know in other countries is transmitted readily, been transmitted in the United States, and there are tests that are already available.

It seems to me that perhaps you need at least a sense maybe of the committee that there is some urgency to move forward with a strategy to intervene at this point in time since it is I guess five years since it was first brought to the BPAC.

DR. DUNCAN: I would respond to that in this way, that up to this point, the lack of a test is mostly being driven by the manufacturers. Now, they are looking for a signal from the FDA that if they put the money into developing the test, it is going to be recommended for screening of all blood, and we are not at that point yet, but I mean these two things sort of need to come forward together I think.

DR. KLEIN: I understand that. I would also add that, of course, the disease is chronic and untreatable, and can be fatal, and if it cross-reacts with visceral leishmaniasis, I think most of us wouldn't care if you omitted those donors, as well.

So, I think there is probably some need maybe to encourage industry to submit something to you that would meet those requirements and to get on with it.

DR. NELSON: I think that is the catch-22 situation is that manufacturers were not clear, that if they met all these requirements, would FDA recommend given the fact that there are a small number of cases, and that is the reason for presenting it.

I hope, it is worthwhile I think for BPAC to express perhaps an opinion that if a test were available that met these criteria, that it certainly would be useful in U.S. blood donors, and that is certainly my feeling.

DR. ALLEN: I share that sense particularly since I mean the demographics, the changing demographics in this country are obvious, and blood collectors in many markets, I think are looking for ways to increase the number of donors from a variety of racial and ethnic, so-called minority communities, Hispanics certainly or Latinos among them. I think this would be an important step to help assure that that can be done safely.

DR. NELSON: We were anticipating when we did this study that we would find some transmitted cases, and, in fact, we found cases, but these 11,000 patients had been exposed to close to 120,000 units of blood, blood or blood products, and they weren't all platelets obviously. In fact, platelets was a small part of it.

But we didn't find it, but we certainly found that there was a problem there in the U.S. population, and one of the cases, one of the six cases had never lived in Latin America. He was from Southern Texas, which Mexican citizens might consider part of the U.S. at this point, but it is an endemic disease in parts of the United States.

DR. NAKASHI: Dr. Nelson, it is our current thinking that if a good test comes along which fits the criteria definitely, it will be recommended. In fact, if you remember, when Rob said early on in his early studies, the early BPAC, in 1999, it was sort of suggested that if a suitable test if available, FDA would recommend testing, so I think from our side, as soon as we see a good test, we will definitely, that's our current thinking at the moment.

DR. NELSON: There were a couple of people

that wanted to make a statement about Chagas. We could open the public hearing.

Dr. David Persing. Keep in mind that we have another item.

Open Public Hearing

DR. PERSING: My name is David Persing. I am Vice President of Molecular Biology at Corixa Corporation, which is a for-profit concern in Seattle, Washington. I am also the Medical Director of the Infectious Disease Research Institute, which is a non-profit organization.

I am wearing my for-profit hat today. I am trained as a clinical pathologist specializing in test development and prior to coming to Corixa, I spent nearly 10 years in clinical practice at the Mayo Clinic developing and implementing specialized tests for human infectious and genetic diseases.

I would like to take this opportunity to mention that Corixa in Seattle has developed a recombinant immunoassay for Chagas disease. This test is based on detection of antibody responses to four complementary immunodominant epitopes that were discovered by serologic expression cloning, by using sera from infected patients. These epitopes are expressed as a single recombinant protein,

called Therapeuticf, consisting of 101 amino acids, including a 6 amino acid hexahistidine tag used for purification. This protein is expressed in an E. coli expression vector and is purified to a single band on SDS page gels.

The TcF antigen has been licensed by three companies for diagnostic purposes - Biokit of Spain, BioMerieux of France, and Diamed of Switzerland. These licenses do not extend to blood donor screening.

These companies have developed kits based on the recombinant protein. The performance of the BioMerieux assay was recently published in the Journal of Clinical Microbiology last month. The sensitivity of the TcF ELISA in 101 patients from Argentina and Brazil was 100 percent.

This group included 27 patients with Chagasic cardiomyopathy, which generally harbor very low numbers of circulating T. cruzi parasites. The specificity of the assay was 98.9 percent of 150 healthy controls, none were positive, but among 39 patients with leishmaniasis, two sera were reactive, which could be consistent with either coinfection with T. cruzi or antigenic cross-reactivity.

By comparison, an assay based on a whole cell sonicate of T. cruzi parasites was reactive in 10 of 39 leishmaniasis patients. Other companies and investigators have tested the TcF protein as a target antigen for blood screening or sera for the presence of antibodies to T. cruzi and reported sensitivity and specificity values at 98 to 100 percent.

In summary, we believe that the TcF recombinant antigen may well serve as the basis for a test with the requisite sensitivity and specificity for blood and organ donor testing in the U.S. As a single recombinant protein, it can be manufactured consistently.

One of the concerns about lysate-based assays is that of specificity, but it also may relate to manufacturing consistency, as was pointed out in an earlier talk, and manufacturing consistency might be enhanced by virtue of making a recombinant protein.

The potential contribution of false positive results due to either leishmaniasis or T. cruzi coinfection in patients with a diagnosis of leishmaniasis, is expected to be extremely low in U.S. blood donors, so our expectation is that

specificity numbers would be higher in the U.S. than in areas endemic for both leishmaniasis and Chagas disease.

Corixa is willing to discuss immediate licensing of its TCF technology to a qualified provider of commercial blood screens in the U.S. and is interested in participating actively in the rapid commercialization of this technology.

Thank you.

DR. NELSON: Thank you very much for that important information. So, the issue is that you would provide or collaborate with a firm that was interested in seeking the IND and meeting the licensing requirements.

DR. PERSING: We are not a test manufacturing company, we don't make ELISA kits, we don't make test kits. We rather license our antigens and technology out to other companies interested in manufacturing.

DR. NELSON: It is hopeful that there are some people in the audience that may work for or represent or know about companies that would be interested in taking this further and getting and IND and getting it licensed.

Kay Gregory.

MS. GREGORY: In the interests of time, I believe most of you have our written statement, so I am going to skip describing the AABB, and I will quickly summarize what our position basically is.

We strongly support FDA's current efforts to encourage the development and implementation of an appropriate screening test for Chagas. We believe that the FDA priorities should be to encourage and sponsor research the production of highly specific screening and appropriate confirmatory assays, and these can be either serologic or nucleic acid based.

Further, we believe there is a need for studies to assess the prevalence in donor populations, and these studies should include an extensive lookback component, so that prior recipients of components from infected donors can be studied.

This will provide estimates of donor infectivity and the infectivity of various transfusable components under current conditions of collection, processing and storage of whole blood and its components.

Thank you.

DR. NELSON: Thanks very much.

Are there any comments from the committee additional about Chagas disease?

If not I would like to move on to the final topic, which was Window Period HIV Cases and Current Estimates of Residual Risk.

Dr. Hewlett from FDA.

Window Period HIV Cases and Current Estimates of Residual Risk (Informational)

Introduction and Background

Indira Hewlett, Ph.D.

DR. HEWLETT: Thank you, Dr. Nelson, and good afternoon, everyone.

In this session, we will be discussing issues surrounding large-scale implementation of individual donation NAT or ID-NAT for whole blood collections. This session is informational in nature, and the FDA is not posing any questions to the committee at this time.

[Slide.]

The specific issue for discussion today is the feasibility of future large-scale implementation of ID-NAT to further reduce the window period and transmissions from this window period of donations screened by pooled sample NAT.

[Slide.]

The topics that will be discussed are the recent window period HIV transmission cases, residual risk estimates, their significance for implementation of ID-NAT and current constraints of implementation of ID-NAT.

[Slide.]

I will be presenting some background information on the issue, followed by Dr. Busch, who will review one of the recent HIV transmissions which occurred in Texas, residual risk estimates, window period, et cetera, and Dr. Leparc who will report on the second transmission which occurred in Florida.

As we all know, viral safety of blood and blood products is ensured by implementation of sensitive tests for the major blood-borne viruses and effective virus removal and inactivation methods for plasma derivatives.

In the case of HIV, antibody screening was implemented for donor testing in 1985, with improved tests being subsequently implemented which reduce the window period to 22 days.

[Slide.]

However, a small number of transmissions continued to occur primarily from window period

donations that were not detected by antibody tests.

In a workshop held in 1994, FDA sought to explore whether nucleic acid testing, or NAT, would be useful in reducing these window period transmissions.

[Slide.]

A large amount of data was presented at this meeting, but experts felt that NAT was not ready for implementation at the time although its development was considered to be a priority.

FDA recommended HIV-1 p24 antigen testing as an interim measure to reduce window period HIV transmissions until sensitive and automated NAT assays became available. Antigen testing further reduced the window period to 16 days, however, the low yield of antigen testing accelerated the development of NAT assays.

[Slide.]

Although NAT assays offer a high degree of sensitivity, they are complex and labor-intensive, and testing of minipools was considered to be a useful interim measure until fully automated and sensitive assays became available for testing of individual donations.

Automation was deemed critical for

large-scale, high-volume testing of individual donations necessary in the blood bank setting.

[Slide.]

In 1999, clinical studies were initiated to evaluate pooled and individual sample NAT for HIV-1 and HCV in whole blood donations. FDA permitted clinical study of this investigational technology on a large scale to evaluates its utility in the intended use setting.

[Slide.]

In February 2002, FDA licensed the Procleix HIV-1/HCV assay, the first pooled and individual sample NAT for semi-automated qualitative detection of HIV and HCV RNA in whole blood.

The test is manufactured by Gen-Probe and distributed by Chiron Corporation.

It is intended for use in screening indication donor samples or pools of plasma comprised of equal aliquots of not more than 16 donations.

[Slide.]

In clinical studies, this assay detected 7 HIV antibody-negative, antigen-negative cases out of 25 million donations tested at 10 pooled and